PHARMACEUTICAL DOSAGE FORMS

Tablets

In Three Volumes

VOLUME 1

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Compressed Tablets

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Compressed tablets are solid dosage forms prepared by compaction of a formulation containing the drug and certain excipients selected to aid the processing and improve the properties of the product. The term compressed tablet generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression. Tablets can be made in many sizes and shapes, with a variety of properties. Tablets are the most widely used of all pharmaceutical dosage forms for a number of reasons. They are convenient, easy to use, and less expensive to manufacture than other oral dosage forms. They deliver the intended dose with a high degree of accuracy.

A number of different types of tablets have been developed for special application. Buccal tablets are designed to dissolve slowly in the buccal pouch. Sublingual tablets are designed to dissolve rapidly beneath the tongue. Chewable tablets are compressed tablets designed to be chewed rather than swallowed; the widely used antacid tablets and some vitamin tablets are of this type. Effervescent tablets are formulated to dissolve with effervescence due to the reaction of citric acid with sodium bicarbonate, or some other effervescent combination in the formulation, when the tablet is placed in water. Certain tablets are made by multiple compression. These include the layer tablets, generally with two layers, but sometimes with three layers. These tablets are designed to enable the separation of incompatible ingredients, to make sustained-release products, or merely for appearance. A compressed coated tablet is prepared by the compression of a tablet within a tablet. As many as two coats can be compressed around a core. Sugar-coated tablets are compressed tablets with sugar coating applied to the tablet. The coating color

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and thickness can vary. Film-coated tablets are compressed tablets with a film coat applied to the tablet. Film coating is the most desirable approach for preparing coated tablets as it is the most economical and involves minimum exposure of the tablet to heat and solvent. When it is desired to prevent the tablet from disintegrating in the stomach, an enteric-coated tablet is prepared. The coating material in this case is insoluble in the acidic environment of the stomach, but readily dissolves in the intestines. Sustained-release tablets are compressed tablets made of a special formulation designed to release the drug over a long period of time. The technology of making special tablets is an extension of the basic technology of the manufacture of compressed tablets. These various special types of tablets are covered in depth in other chapters of this volume. In the sections that follow, reference to equipment and materials will frequently be made by trade name. The description and sources of materials are listed at the end of the volume.

I. Methods of Manufacture

Tablets are made by compressing a formulation containing a drug or drugs and excipients on a tablet press. The basic functional unit of the tablet press is a set of tooling consisting of a die and an upper and lower punch. The tablet press is designed to have a hopper for holding and feeding the granulation, a feeding mechanism for feeding the granulation to the die cavity, provision for placement of punches and dies, and cam tracks for guiding the movement of punches. Tablet presses are of two basic types, the single-station or single-punch press and the multistation rotary press. The schematic of the tablet compression process on a single-punch is shown in Figure 1. The first stage is the filling cycle during which the lower

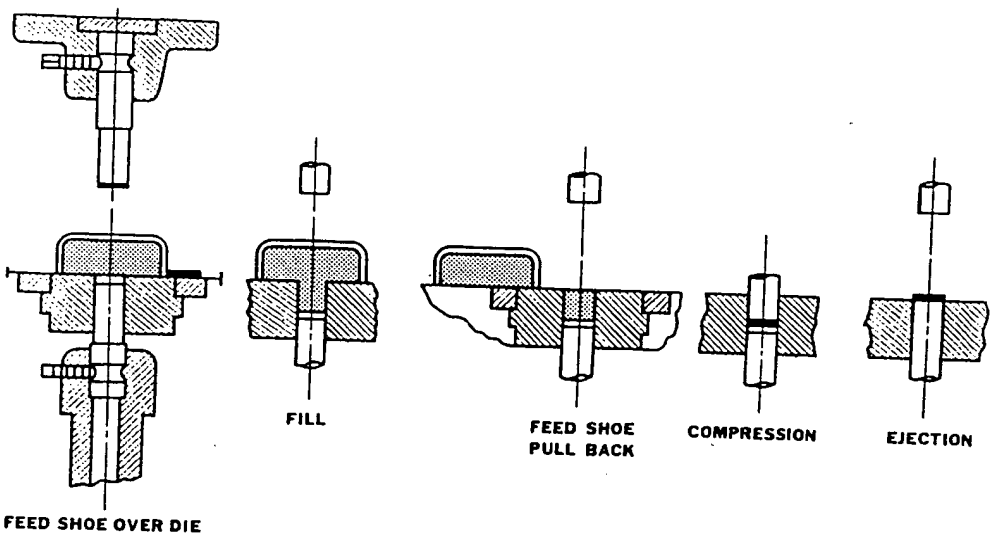

Figure 1. Schematic diagram of the compression process in a single-punch tablet press. (Courtesy, Vector Corporation, Hiawatha, Iowa.)

punch is lowered to a preset point to form a cavity in the die to provide a volume corresponding to the correct fill weight for the tablet. Next the feed shoe is pulled out of the way, and the upper punch descends into the die to compress the tablet. Then the lower punch is raised flush with the surface of the die table so that the feed shoe can eject the tablet as it comes over the die for another fill cycle.

Tablet presses operate at production rates ranging from a few to a few thousand tablets per minute. Hence, a tablet formulation must first be prepared in a form suitable for compression on a tablet press. This process is referred to as the preparation of a granulation or, simply, granulation. The resulting product is called the tablet granulation or again, simply, the granulation.

A granulation must have good flow properties for precise volumetric feeding of the material to the die cavity, compressibility to form the compact, and lubricant properties for ejection of the tablet. The methods used for preparing tablet granulations are wet and dry granulation and direct compression. The sequential steps in the manufacture of tablets by each of these processes is shown in Table 1. The first step in each method is to prepare a mixture of the drug and some or all of the excipients, depending upon the method. The wet and dry granulation processes are designed to improve the flow and compressibility of powders that would otherwise be unsuitable for making tablets. When the formulation can be designed to have satisfactory flow and compressibility, the ingredients are mixed and directly compressed into tablets. This latter process is referred to as direct compression.

Each method has its advantages and disadvantages, specific applications, and restrictions. The choice of methods depends upon a number of factors, the most important being the properties and the dose of the drug. Other factors include the choice of available equipment and relevant practical and regulatory concerns. Direct compression is the simplest method and should be evaluated for new products where its use may be feasible. Wet granulation is the most widely used method. The application of the dry granulation method is limited to situations where neither wet granulation nor direct compression can be used.

A. Properties of Tablets

Whatever method of manufacture is used, the resulting tablets must have satisfactory properties. The attributes of a good tablet are as follows:

1. The tablet must be sufficiently strong and resistant to abrasion to withstand handling during manufacture, packaging, shipping, and use. This property is measured by two tests, the hardness test and the friability test.
2. The drug in the tablet must be bioavailable. This property is monitored by two tests, the disintegration test and the dissolution test. However, the bioavailability of a drug from a tablet or other dosage form is a very complex problem, and the results of these two tests do not of themselves provide an index of bioavailability.
3. The tablets must be uniform in weight and in the drug content of individual tablets. This is measured by the weight variation test and the content uniformity test.
4. The tablets must be elegant in appearance and must have the characteristic color, shape, and other markings that identify the product. The marking is usually a monogram of the manufacturer. Many tablets also have the National

Table 1

Steps in the Different Methods of Tablet Manufacture

Wet granulation	Dry granulation	Direct compression
1. Milling of drugs and excipients	1. Milling of drugs and excipients	1. Milling of drugs and excipients
2. Mixing of milled powders	2. Mixing of milled powders	2. Mixing of ingredients
3. Preparation of binder solution	3. Compression into large, hard tablets, to make slugs	3. Tablet compression
4. Mixing of binder solution with powder mixture to form wet mass	4. Screening of slugs	
5. Coarse screening of wet mass using 6 to 12 mesh screen	5. Mixing with lubricant and disintegrating agent	
6. Drying of moist granules	6. Tablet compression	
7. Screening of dry granules through 14 to 20 mesh screen		
8. Mixing of screened granules with lubricant and disintegrant		
9. Tablet compression		

Drug Code number corresponding to the listing of the product in the National Drug Code of the U.S. Food and Drug Administration. Another marking that may appear on some tablets is a score. It is intended to permit the breaking of tablets into two equal parts for the administration of half a tablet; however, it has been shown that substantial variation in drug dose can occur in the administration of tablets manually broken.

5. The tablets must retain all of the functional attributes, which include drug stability and efficacy.

B. Unit Processes

The properties of a tablet are affected by both the formulation and the method of manufacture, and between these two factors there is a high degree of interrelationship. A suitable formulation is critical to the manufacture of satisfactory tablets. However, the formulation must be designed according to the needs, advantages, and limitations of the manufacturing method and equipment used. The major unit processes involved in the manufacture of tablets are: solid-solid mixing, solid-liquid mixing, milling or size reduction, drying, and compaction. The selection of the formulation components and equipment is done to optimize the efficiency of the unit processes involved. Generally, it is necessary to use equipment already available in the manufacturing facility, and the formulation would need to be adapted to the available process and equipment. Certain other general considerations should also be noted. Since tablet manufacture involves the processing of powders, a high degree of control of the temperature and humidity of the work area is necessary. Normal air-conditioning can provide the needed environment in most cases. However, with some drug products, humidity may have to be controlled to lower levels than is feasible with standard air-conditioning equipment. There is also a high potential of cross-contamination between products in the processing of powders. Therefore, both the design of the area as well as the working procedures must be suitably designed for this purpose. Operators working in the area must be protected from the dust of potent drugs and other powders and from solvent vapors.

II. Wet Granulation

The preparation of granulations for tableting by wet granulation is the oldest method and still the most widely used. Before dry compaction became a viable process, wet granulation was—for all practical purposes—the only method available. However, it is laborious, involving considerable material handling, as well as several processing steps, and therefore it is costly. The method nevertheless continues to find extensive application for a number of reasons. One reason is that, because of its universal use in the past, the method persists with established products and with new products where—for one reason or another—it cannot be replaced by direct compression methods. Although a number of these products could now be made by direct compression, to do so would require a change in ingredients or, at a minimum, a change to new forms of previously used excipients. A change of this nature would be considered a major modification requiring a careful review to evaluate the need for additional studies of product stability, safety, and efficacy, as well as the impact of pertinent practical and regulatory considerations. Since

extensive data are likely to have been accumulated on existing products, there is understandable reluctance on the part of the drug industry to undertake such changes unless they are dictated by compelling reasons. A second reason for the use of the method is that some formulators prefer to use wet granulation to assure content uniformity in the resulting tablets. This judgment depends to a great extent upon the personal experience of the formulator in the previous use of different tableting methods. A third reason is that wet granulation is the process of choice to use in tablet formulations of many high-dose drugs where direct compression—because of the necessity to add a considerable amount of filler to facilitate compaction—becomes unfeasible because of the resulting increase in tablet size.

Another advantage of wet granulation is that the drying cycle of the process can be manipulated to produce a dry granulation with a low moisture content. When such low moisture content is not attainable with some direct compression formulations because of the excessive moisture content of the components, the formulation would have to be subjected to a drying cycle, thereby losing much of the benefit of economy of processing.

A. Advantages of Wet Granulation

A comparison of the sequential steps in the manufacture of tablets by different methods is shown in Table 1. It is evident that direct compression would be a much simpler and less expensive process. It is therefore important to understand the advantages of wet granulation in order to appreciate its usefulness. The purpose of granulation is to enlarge the particle size of a powder and obtain uniform particles which will flow readily through the tablet machine hopper and feed frames into the dies. This results in a number of improvements in the properties of the powder with regards to tableting.

1. The cohesiveness and compressibility of powders is improved due to added binder which coats the individual powder particles, causing them to adhere to each other so they can be formed into agglomerates, called granules. Thus by this method, the properties of formulation components are modified to overcome their tableting deficiencies. During the compaction process, granules are fractured, exposing fresh, clean powder surfaces, and this also improves compressibility. Lower pressures are therefore needed to compress tablets—resulting in improvements in tooling life and machine wear.

2. High-dosage drugs having poor flow or compressibility properties must be prepared by wet granulation to obtain suitable flow and cohesion for compression. In this case, the proportion of binder required to impart adequate compressibility and flow is much less than the proportion of dry binder needed to produce a tablet by direct compression.

3. Good distribution and uniform content for soluble low dosage drugs and color additives is obtained if these are in the binder solution of a wet granulation. This represents a distinct advantage over direct compression, where content uniformity of drugs and uniform color dispersion can be a problem.

4. Wet granulation prevents segregation of components of a homogeneous powder mix during processing, transferring, and handling. In effect, the composition of each granule becomes fixed and remains the same as—or very nearly that of—the powder mixture at the time of liquid-binder addition.

5. The dissolution rate of a hydrophobic drug may be improved by wet granulation with the proper choice of solvent and binder.

B. Limitations of Wet Granulation

The greatest disadvantage of wet granulation is its cost. It is an expensive process because of the labor, time, equipment, energy, and space requirements. However, a number of improvements have been made in recent years to improve the wet granulation method and reduce its cost. These include:

A solid-liquid twin-shell blender with a dispersion bar to add the binder solution and produce agglomerates, with a heated jacket and vacuum take-off to facilitate and hasten drying. This unit, properly operated, can produce a completed granulation.

A fluidized bed dryer equipped with a spray head to add the binder and other components, granulating and drying simultaneously.

Mixers such as the Lodige and the Diosna, which provide efficient and rapid solid-solid and solid-liquid blending, reducing the time and material handling involved.

Wet granulation of moisture sensitive drugs can usually be overcome by the use of anhydrous solvents with solvent-soluble binders to form the wet mass to produce the granulation. If the solvent presents a health and/or explosion hazard, explosion-proof equipment and adequate air and vapor handling equipment must be used to remove the vapor. The use of soluble dyes in wet granulations often causes migration of the dyes during the drying cycle. As the solvent evaporates, materials soluble in it, including dyes, tend to migrate to the surface of the granules, thus causing unequal distribution of color. Although some redistribution occurs during subsequent mixing and milling, some color mottling of tablets on compression may nevertheless result. This can be overcome by the use of insoluble lake dyes which do not migrate in either aqueous or solvent granulations.

An inherent limitation of wet granulation is that any incompatibility between formulation components will be aggravated by the granulating solvent bringing them into close contact.

C. Process Parameters in Wet Granulation

The various steps involved in the wet granulation process have a significant effect on the tableting properties of the resulting granulation. It is therefore important to understand these process parameters in terms of their impact on process design and selection of formulation components. Essential to the wet granulation process are the following operations and processes:

Preparation of the powder mixture with screening and mixing
Addition of binder solution and mixing with powder to proper wetness
Drying the solid-liquid blend
Milling the dry granulation to size
Addition of lubricant, glidant, and/or other excipients prior to compression

Wet granulation consists of moistening the mixture of active ingredient and diluent with the granulating liquid comprising the binder in solution in water, alcohol, or mixture of these two, or any other acceptable liquid to moisten and bind the powders together by causing the particles to adhere to each other. The wet mass produced by mixing the liquid with the solid should have a doughlike consistency so that a handful can be formed into shape without crumbling. When pressed into a ball with the hands and broken in half, it should give a clean fracture without sticking or crumbling. If the mass has a tendency to stick or not break clean, the granulation is usually too wet. If the mass crumbles or breaks into pieces it is too dry.

The wet mass is then passed through a standard 4, 6, 8, or 12 mesh screen, depending upon the ease with which the wet mass can be forced through the screen. Starting with a 12 mesh screen in an oscillating granulator or a Fitzpatrick mill with the knife edges forward and a Fitzpatrick screen, the smallest opening through which the wet mass will pass should be determined. It is desirable to use the smallest opening possible so that small granules can be obtained, which facilitate drying because of their greater surface area and smaller individual mass.

III. Tablet Excipients

A tablet formulation contains a number of excipients in addition to the active ingredients. Each excipient is selected to meet the needs of processibility and product use. The major types of excipients used are fillers or diluents, binders, disintegrating agents, and lubricants—which are present in nearly all tablet formulations. Other excipients may be needed for specific purposes. Colors are added to a large proportion of tablets to provide a characteristic appearance and also to improve quality assurance by minimizing the chances for product mix-up during in-process stages of manufacture. Glidants and antiadherents are needed in some formulations. Sweeteners and flavors are needed in chewable tablets.

A. Fillers

Fillers or diluents are used to increase the bulk of the tablet so as to enable a formulation to become suitable for compression. It is generally not feasible to make tablets with a weight of less than about 70 mg. In addition to lending bulk to the formulation, fillers are selected to improve the binding and flow properties of the formulation. It is essential that fillers be inert and stable. A list of the more commonly used fillers in wet granulation is shown in Table 2. Fillers used in direct compression are discussed in detail in Section IV.C.

Lactose, also known as milk sugar, is probably the most widely used tablet diluent or filler. The solubility and sweetening power of lactose is lower than that of other sugars. It is obtained by crystallization from whey, a milk by-product of cheese manufacture. The most common form commercially available is α-lactose monohydrate, which is produced by crystallization from supersaturated solutions below 93.5°C. If crystallization occurs above 93.5°C, the β-anhydride is obtained. This form is also commercially available but in lesser quantities. Lactose for tableting purposes is available as crystalline and spray-dried products. The spray-dried form is used largely in direct compression. For the manufacture of tablets by the wet granulation procedure, crystalline lactose is used. It is available as a

Table 2

Fillers Commonly Used in Wet Granulation Formulations

Insoluble fillers	Soluble fillers
Calcium sulfate NF	Lactose
Dibasic calcium phosphate NF	Sucrose
Tribasic calcium sulfate NF	Mannitol
Starch	Sorbitol
Calcium carbonate	
Microcrystalline cellulose	
Modified starches	

fine impalpable powder in two particle size ranges, Impalpable Powder in the particle size range of 200 to 225 mesh and Impalpable C Powder in the size range of 300 to 325 mesh—as compared to spray-dried lactose which is available in the particle size range of 100 to 200 mesh. Lactose tends to crystallize in pure form, leaving impurities behind in the mother liquor. As crystalline lactose, it does not have as great a tendency to turn brown, as occurred with the earlier supplies of spray-dried lactose. Although contaminants are removed during the manufacturing process, the possibility of browning still remains. Lactose has very few incompatibilities and can be used with most drugs. The form most generally used is the Impalpable Powder. The Impalpable C Powder is used for molded tablets.

Sucrose is used generally as a tablet diluent in the form of confectioners sugar, which is a finely ground sucrose containing 3% starch to prevent caking. It is available as 4× and 6× powders representing different degrees of fineness: the 4× has a particle size such that approximately 90% passes through a 200 mesh screen, and approximately 80% of the 6× passes through a 325 mesh screen. Sucrose is used, in some cases, to impart sweetness to chewable tablets. But its more important use in wet granulation is to impart hardness to tablets. Used in the dry state in the tablet, it binds to a moderate hardness, depending upon the amount used and the solubility of the other ingredients. If a mixture of alcohol and water is used to granulate, softer granules are produced than if water alone is used. Sugar should be used in small amounts in tablet formulations since it has the disadvantage of being somewhat hygroscopic. If it is used in sufficient quantities the tablets will harden with time, which would interfere with the dissolution of the drug from the tablet. Sucrose, like lactose, will turn brown if used with alkaline materials. Some of the directly compressible forms of sucrose, such as Di-Pac and Nu Tab, can be used with granulations prepared by the wet process for imparting hardness to the tablet. However, this can be done only with white granulations since the techniques for adding color to this type of formulation have not been developed.

Dextrose has found some use in wet granulation as a diluent as well as a binder. It can be used essentially in the same way as sucrose, but is not available in fine powder form such as confectioners sugar. It is also not as sweet as sucrose,

and tablets containing dextrose tend to increase in hardness with time, especially if the anhydrous form of dextrose is used.

Mannitol is another sugar that is used particularly in chewable tablets. It is a white, odorless, pleasant-tasting crystalline powder which is essentially inert and nonhygroscopic. Mannitol is the preferred tablet diluent for the production of chewable tablets because of its pleasant, slightly sweet taste giving tablets a smooth, melt-down mouth-feel; its negative heat of solution gives it a cool taste. Mannitol may be granulated with a variety of granulating agents. It has been shown that mannitol requires more granulating solution than either sucrose or lactose and approximately the same amount as dextrose. This is shown in Table 3. The moisture content of these granulations after overnight drying at 140 to 150°F for sucrose, dextrose, and mannitol was less than 0.2%, except for the dextrose granulations made with 10% gelatin and 50% glucose, in which the moisture content was 1.15% and 0.26%, respectively. In all of the lactose granulations, the moisture was between 4 and 5%. Mannitol and sucrose were the lowest, having about the same moisture content. However, it was found that mannitol, although it required more granulating solution, generally gave a softer granulation than did sucrose or dextrose. Lactose granulations more closely resembled mannitol.

Table 3

Granulating Solution Required by 3000 g of Diluent

Volume of granulating solution required (ml)	Diluent			
	Sucrose	Lactose	Dextrose	Mannitol
10% Gelatin	200	290	500	560
50% Glucose	300	325	500	585
2% Methocel (400 cps)	290	400	835	570
Water	300	400	660	750
10% Acacia	220	400	685	675
10% Starch paste	285	460	660	810
50% Alcohol	460	700	1000	1000
10% PVP[a] in water	260[b]	340[b]	470[b]	525
10% PVP[a] in alcohol	780[b]	650[b]	825[b]	900
10% Sorbitol in water	280[b]	440[b]	750[b]	655

Source: Taken in part from the Technical Bulletin, Atlas Mannitol, ICI Americas, Inc., Wilmington, Del., 1969.

[a] Polyvinylpyrrolidone.

[b] Derived by one of the authors (F.J.B.), not from source noted above.

Calcium sulfate is an insoluble, nonhygroscopic, mildly abrasive fine powder. It is an inexpensive filler that can be used as a diluent for acidic, neutral, and basic compounds. It has a high absorption capacity for oils. However, it is essentially nonadsorptive of organic bases, so that drug-excipient interactions due to sorption are minimized with the large majority of drugs. It can be used with a wide range of drugs since it has few incompatibilities. When granulated with polymer solutions, the tablets will generally not harden with time. The use of sugar solutions for granulation should be avoided as the resulting tablets will tend to harden with time.

Example 1: Vitamin B_{12} Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Vitamin B_{12}	55 μg[a]	0.55 g[a]
Calcium sulfate	110 mg	1100 g
Sucrose	20 mg	200 g
10% Pregelatinized starch solution	q.s.	q.s.
Sta-Rx starch	10 mg	100 g
Avicel PH 101	12 mg	120 g
Sterotex	0.75 mg	7.5 g

[a] Includes 10% manufacturing excess.

Mix the sucrose and calcium sulfate. Dissolve the vitamin B_{12} (cyanocobalamin) in about 50% of the pregelatinized starch solution to be used, and add it slowly with mixing to the sucrose and calcium sulfate mixture. Allow to mix 15 min. Add sufficient of the remaining starch solution to granulate. Add slowly and allow to mix 30 min. Pass the wet mass through a 14 mesh screen and dry the granules in an oven at 120 to 130° F. When dry, pass through a 20 mesh screen. Mix the Sta-Rx, Avicel, and Sterotex and pass through an 80 mesh screen. Add to the granulation and mix in a tumble mixer for 20 min. Compress to weight with 1/4-in. standard concave punches.

Dicalcium phosphate is an insoluble, neutral, nonhygroscopic, mildly abrasive fine white powder. The unmilled dihydrate form of this material is used extensively in direct compression. Its properties are similar to those of calcium sulfate, but it is more expensive and is used only to a limited extent in wet granulation (Example 2). It should not be used with strong acid salts of weak organic bases. If inorganic acetate salts are present in the formulation, the tablets are likely to develop an acetic acid odor on standing. It can be used with most salts of organic bases, such as antihistamines, and also with water-soluble vitamins, chlorothiazides, barbiturates, and similar drugs.

Tricalcium phosphate is an insoluble, slightly alkaline, nonhygroscopic, abrasive fine white powder. It is used to a limited extent in wet granulation. Its use should be avoided with strong acid salts of weak organic bases and when inorganic acetate salts are present in the formulation. Because of its alkalinity, it should also not be used with water-soluble vitamin B salts or with certain esters such as vitamin E

Example 2: Sodium Phenobarbital Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Sodium phenobarbital	64.8 mg	648 g
Dicalcium phosphate	60.6 mg	600 g
Starch	12.0 mg	120 g
10% Polyvinylpyrrolidone in 50% alcohol	q.s.	q.s.
Carbowax 6000 (fine powder)	3.5 mg	35 g
Avicel	7.5 mg	75 g

Mix the sodium phenobarbital, dicalcium phosphate, and starch and moisten with the PVP hydroalcoholic solution to proper wetness to granulate. Pass the wet mass through a 14 mesh screen or through a #2B Fitzpatrick Mill perforated plate at medium speed, hammers forward. Dry the granulation on trays in a forced-air oven overnight at 130 to 140°F. Pass the dry granulation through a 20 mesh screen. Mix the Carbowax 6000 with the Avicel and pass the mixture through an 80 mesh screen. Add this to the dried granulation and mix in a tumble mixer for 15 to 20 minutes. Compress to weight with 1/4-in. flat-face punches.

acetate. It can be used with most salts of organic bases, chlorothiazides, and barbiturates. There is more variation in alkalinity and in particle size between various sources of tribasic calcium phosphate than with dibasic calcium phosphate. It is also more difficult to granulate than either calcium sulfate or dibasic calcium phosphate.

Starch is a naturally occurring diluent which is bleached white and can be obtained in varying degrees of whiteness. The material most frequently used is cornstarch. It is a multiple-purpose product in that it can also be used as a disintegrating agent and as a binder in the form of starch paste. It has the disadvantage of having compressibility too poor to make tablet of sufficient hardness. It also tends to expand after compression. Therefore, it is not used to any great extent as a filler in compressed tablets; it is used to a greater extent as a diluent in capsules. Starch is used widely as a disintegrant in the concentration range of 5 to 20%. In this application, starch may be added to the powder prior to wet granulation, or it may be added dry to a granulation prepared by the wet process. Starch has few incompatibilities, but it should not be used as a diluent for strongly acidic compounds since it will partially hydrolyze on drying.

Microcrystalline cellulose is a white, insoluble, neutral, nonreactive, free-flowing, versatile filler. Used in sufficient quantity, usually 10 to 20%, it also serves as a dry binder and disintegrating agent. It is widely used in direct compression. It has an extremely low coefficient of friction, both static and dynamic, so that it has no lubricant requirement itself. However, when more than 20% of drugs and other excipients is added, lubrication is necessary. It has few if any incompatibilities and can be used with other diluents with excellent results. Microcrystalline cellulose is available in two grades, Avicel PH 101, which was the original product, and Avicel PH 102, which is a partially agglomerated product with

large particle size distribution and slightly better fluidity with no significant decrease in compressibility. It has been suggested that both Avicel PH 101 and PH 102 can be used advantageously in wet granulation. A level of 5 to 15% is recommended. When used as a wet-massing adjunct, the wicking action of microcrystalline cellulose promotes rapid, even wetting of the powder mix. Its ability to retain water makes the wet mass less sensitive to overwetting due to excess of granulating fluid. The milling of the wet mass is easier due to less clogging of the screen. This produces a more uniform granulation, which is readily dried with reduced case hardening. This is particularly useful with some materials which, when wetted or overmixed, become a chalky, claylike mass clogging screens during the wet milling process. When dried, these granules often are hard and resist disintegration. A material in which this problem may be encountered is calcium carbonate, as shown in the following examples.

Example 3

Ingredient	Quantity
Calcium carbonate	1000 g
Water	300 ml

Example 4

Ingredient	Quantity
Calcium carbonate	1000 g
Avicel PH 101	100 g
Water	300 ml

The material of Example 3 produces a sticky mass whereas Example 4 produces a nonsticky mass which can be granulated through a 12 mesh screen.

Microcrystalline cellulose may be added dry to a granulation prepared by the wet method to improve bonding and reduce capping and friability.

Example 5

	Quantity per tablet	Quantity per 20,000 tablets
Drug	500 mg	10,000 g
Starch	9.83 mg	197 g
Polyvinylpyrrolidone (PVP-K30, 8% alcohol solution)	18.58 mg	372 g
Avicel PH 101	60 mg	1,200 g
Calcium stearate	4 mg	118 g

Mix the drug and starch; granulate with the alcoholic solution of PVP. Pass the wet mass through a 12 mesh screen and dry at 120 to 130°F. Pass the dry granulation through a 16 mesh screen. Mix with Avicel and calcium stearate previously screened through a 40 mesh screen. Compress using 7/16-in. standard concave tooling.

Because of its low bulk density, tablets with a higher proportion of microcrystalline cellulose tend to have a greater porosity. Other examples in the chapter will also serve to illustrate the use of these fillers in wet granulation formulations.

B. Binders

The appearance, elegance, and ease of compression of tablets are directly related to the granulation from which the tablets are compressed. Granulations in turn are dependent—on the materials used, processing techniques, and equipment—for the quality of the granulation produced. Of these variables, none is more critical than the binder used to form the granulation—for it is largely the binder which is fundamental to the granulation particle size uniformity, and adequate hardness, ease of compression, and general quality of the tablet.

Direct compression, facilitated by techniques such as induced die feeding and by the availability of compressible materials for admixture with medicinal agents, is a streamlined and more economical method of tablet manufacture than the wet granulation approach. However, direct compression cannot completely replace wet granulation in the immediate future. Wet granulation is necessary to produce uniformly colored tablets, tablets containing potent drugs of low dosage level with minimal intertablet variation, chewable tablets where mouth-feel is enhanced by

Table 4

Binders Used in Wet Granuation

Starch	5-10% w/v Aqueous paste
Pregelatinized starch	5-10% Added dry to powder
Gelatin	2-10% Aqueous solution or 2% in starch paste
Polyvinylpyrrolidone	5-20% Aqueous or alcoholic solution
Methylcellulose (various viscosity grades)	2-10% Aqueous solution
Sodium carboxymethylcellulose (low-viscosity grade)	2-10% Aqueous solution
Ethylcellulose (various viscosity grades)	5-10% Alcohol or hydroalcoholic solution
Polyacrylamides (Polymer JR)	2-8% Aqueous solution
Polyvinyloxoazolidone (Devlex)	5-10% Aqueous or hydroalcoholic solution
Polyvinyl alcohols	5-20% Aqueous solutions

wet granulation, and special granulations such as sustained-release and compression-coated tablets.

Binders are either sugars or polymeric materials. The latter fall into two classes: (1) natural polymers such as starches and gums, including acacia and tragacanth, and (2) synthetic polymers such as polyvinylpyrrolidone and methyl cellulose. Binders of both types may be added dry to the powder mix, and the mixture wetted with water, alcohol, and alcohol-water mixtures—or the binder may be put into solution in the solvent and added. The latter method, using the solution of the binder, requires much less of the binding materials to achieve the same hardness than if added dry. In some cases, it is not possible to get granules of sufficient hardness using the dry method. A list of the binders used in wet granulation is shown in Table 4.

Starch, probably the most commonly used binder in the past, has been starch in the form of starch paste, typically used in concentrations of 5 or 10%. A simple way to make starch paste is to suspend the starch in 1 to 1 1/2 parts of cold water, than add 2 to 4 times as much boiling water with constant stirring. The starch sweels almost immediately to make a translucent paste which can then be diluted with cold water to the desired concentration. Starch paste may also be prepared by suspending the starch in cold water and heating to boiling in a steam-jacketed kettle with constant stirring. Starch paste is a versatile binder, yielding granules and tablets which disintegrate readily (Examples 6 and 7). It is also an excellent carrier for dyes which have been dissolved in the cold water used in making the paste. Granulation of the powder mix with colored starch paste produces uniform distribution of color with little or no tendency for the colors to migrate to the surface of the granules on drying. Starch paste generally forms firm yet soft and cohesive granules. One reason why starch paste is much used is that it is an excellent binder for such common diluents as calcium sulfate, dibasic calcium phosphate, lactose, and starch. It is neutral and nonreactive and can be used with many active ingredients.

Example 6: Phenobarbital Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Phenobarbital	65 mg	650 g
Lactose (fine powder)	40 mg	400 g
Starch (as starch paste)	4 mg	40 g
Starch (dry)	10 mg	100 g
Talc	10 mg	100 g
Mineral oil, 50 cps	4 mg	40 g

Mix the phenobarbital and lactose and moisten with 10% starch paste to proper wetness. Granulate by passing through a 14 mesh screen and dry at 140° F. When dry, pass through a 20 mesh screen; add the dry starch and talc; mix well; and, finally, add the mineral oil, mix again, and compress using 9/32-in. standard cup punches.

Example 7: Thiamine Hydrochloride Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Thiamine hydrochloride	55 mg[a]	550 g[a]
Lactose (fine powder)	200 mg	2000 g
Tartaric acid (fine powder)	5 mg	50 g
Starch (as starch paste)	6 mg	60 g
Sterotex	8 mg	80 g
Alginic acid	10 mg	100 g

[a] Includes 10% excess thiamine hydrochloride.

Mix the thiamine hydrochloride, lactose, and tartaric acid and moisten with starch paste. Pass through a 14 mesh screen to granulate. Dry at 120° F and reduce through a 20 mesh screen. Add the alginic acid and Sterotex; mix well, and compress using 3/8-in. standard concave punches.

Pregelatinized starch can be used in place of starch as starch paste. Its binding properties are slightly greater than starch paste, and it offers the advantage of being soluble in warm water without boiling. It is available from most of the major starch companies. Pregelatinized starch may also be used as a binder by adding it dry to the powder mix and wetting with water to granulate.

Example 8: Aminophylline Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Aminophylline	100 mg	1.0 kg
Tricalcium phosphate	50 mg	0.5 kg
Pregelatinized starch	15 mg	0.15 kg
Water	q.s.	q.s.
Talc	30 mg	0.3 kg
Mineral oil, light	2 mg	0.02 kg

Mix the aminophylline, tricalcium phosphate, and starch and moisten with water. Pass through a 12 mesh screen and dry at 110° F. Size the dry granules through a 20 mesh screen; add the talc and mix. Add the mineral oil, mix for 10 minutes, and compress using 5/16-in. deep cup punches for enteric coating.

Approximately 4 times more starch is required to achieve the same tablet hardness as when using starch in solution. Using this method produces tablets with shorter disintegration times. If the powder mix is such that starch paste does not give sufficiently firm granules, 2 to 5% gelatin may be added to it.

Gelatin, if a still stronger binder is needed, may be used as a 5 to 10% solution. Gelatin solutions should be made by first allowing the gelatin to hydrate in cold water for several hours or overnight, then heating the solution to boiling. Gelatin solutions must be kept hot until used or they will gel on cooling. Although gelatin (2 to 10% aqueous solution) has been used extensively as a binder, it is being used less with the advent of new synthetic polymers. Gelatin has a tendency to produce hard granules similar to those produced by sucrose solutions. It has the disadvantage that tablets made with gelatin tend to harden with age.

Sugars such as sucrose or dextrose form the hardest granules. They are typically used as solutions with concentrations of 50 to 85%.

Example 9: Barium Sulfate Tablets

Ingredient	Quantity per tablet	Quantity per 5,000 tablets
Barium sulfate	1.35 g	6750 g
Avicel PH 101	0.335 g	1675 g
Stearic acid	0.0017 g	8.5 g
Syrup (70% w/w)	0.317 g	1583 g
Equivalent to sugar	0.222 g	1108 g

Granuate barium sulfate with syrup. Pass the wet mass through an 8 mesh screen and dry at 120 to 130° F. Pass the dry mass through a 14 mesh screen. Mix the granulation with Avicel PH 101 and stearic acid. Compress using 1/2-in. standard concave punches.

They are also good carriers of soluble dyes, producing granulations and tablets of uniform color. Sugar syrup is used to granulate tribasic calcium phosphate, which usually requires a binder with greater cohesive properties than starch paste. Some of the other compounds for which sugar syrup is indicated include aminophylline, acetophenetidin, acetaminophen, and meprobamate.

Acacia solutions have been used as granulating agents in the past, but acacia has now been largely replaced by recently developed polymers (Example 10). Gum acacia produces hard granules but without producing tablets of increasing hardness with time, as is the case with gelatin. One of the disadvantages of acacia is that it is a natural product and is often highly contaminated with bacteria—which makes it objectionable as a binder. Gum tragacanth is another natural gum which has been used in 5 to 10% solutions as a tablet binder. It does not produce granulations as hard as acacia solutions. Like acacia, it often has a high bacterial content. It has never been a popular binder and is seldom used today. Among the synthetic polymers which have replaced some of the older binders are: (1) polyvinylpyrrolidone;

Example 10: Theobromine-Phenobarbital Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Theobromine USP	325 mg	3.25 kg
Phenobarbital USP	30 mg	300 g
Acacia (as 10% solution)	8 mg	80 g
Polyethylene glycol 6000	4 mg	40 g
Talc	8 mg	80 g
Stearic acid	0.8 mg	8 g
Starch	25 mg	250 g

Mix the theobromine and phenobarbital. Dissolve the acacia in hot water. Next, dissolve the PEG 6000 in the acacia solution and use it to wet the theobromine-phenobarbital mixture; pass the wet mass through a 12 mesh screen. Dry in an oven at 130 to 140° F overnight. Force granules through a 16 mesh screens; add the starch, talc, and stearic acid and compress using 13/32-in. standard concave punches.

(2) methylcellulose; (3) sodium carboxymethylcellulose; (4) ethylcellulose; (5) hydroxypropylmethylcellulose; (6) polyacrylamides; (7) polyvinyloxoazolidones.

Polyvinylpyrrolidone (PVP) has become a popular binder. This compound, first developed as a plasma substitute in World War II, is unreactive and has the advantage of being soluble in both water and alcohol.

Example 11: Chewable Antacid Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Aluminum hydroxide (dried gel)	400 mg	4.0 kg
Magnesium hydroxide (fine powder)	80 mg	0.8 kg
Sucrose, confectioners	20 mg	0.2 kg
Mannitol (fine powder)	180 mg	0.8 kg
Polyvinylpyrrolidone (as 10% solution)	30 mg	0.3 kg
Magnesium stearate	15 mg	0.15 kg
Cab-O-Sil M-5	4 mg	0.04 kg
Oil of peppermint	0.2 mg	0.002 kg

Mix the first four ingredients and moisten with a 10% PVP solution in 50% ethanol. Granulate by passing through a 14 mesh screen. Dry at 140 to 150°F. Size through a 20 mesh screen, add the oil of peppermint mixed with the Cab-O-Sil and finally the magnesium stearate; mix well and compress using 1/2-in. flat-face bevel-edge punches.

Although it has a tendency to be slightly hygroscopic, tablets prepared with it do not, as a rule, harden with age. Generally, it is better to granulate insoluble powders with aqeuous or hydroalcoholic solutions of PVP and to granulate soluble powders with PVP in alcohol solution. Effervescent tablets comprising a mixture of sodium bicarbonate and citric acid can be granulated with PVP in anhydrous alcohol since no acid-base reaction occurs in this anhydrous medium. Anhydrous ethanol should be used in this granulation and not anhydrous isopropanol, since the latter leaves a trace of its odor in tablets, no matter how—or how long—the granulation has been dried. A concentration of 5% PVP in anhydrous ethanol produces a granulation of good compressibility of fine powders of sodium biacrbonate and citric acid, and makes for vigorous effervescence and rapid dissolution of the resulting tablets. Polyvinylpyrrolidone is also an excellent binder for chewable tablets, especially aluminum hydroxide antacid chewable tablets. The inclusion of 2 to 3% of glycerine (based on the weight of the final tablet) tends to reduce hardening of these tablets with age. It is a versatile and excellent binder used in approximately the same concentration as starch, but it is considerably more expensive.

Methylcellulose in aqueous solutions of 1 to 5%, depending on the viscosity grade, may be used to granulate both soluble and insoluble powders. A 5% solution produces granulations similar in hardness to 10% starch paste. It has the advantage of producing granulations which compress readily, producing tablets which generally do not harden with age. Methylcellulose is a better binder for soluble excipients such as lactose, mannitol, and other sugars. It offers considerable latitude in binding strength because of the range of viscosity grades available. Low viscosity grades, 10 to 50 cps, allow for higher working concentrations of granulating agent than higher viscosity grades, such as the 1000 to 10,000 cps grades.

Sodium carboxymethylcellulose (sodium CMC) in concentrations of 5 to 15% may be employed to granulate both soluble and insoluble powders. It produces softer granules than PVP, and the tablets have a greater tendency to harden. Sodium CMC is incompatible with magnesium, calcium, and aluminum. Although sodium CMC produces soft granules which generally compress well, it produces tablets with relatively long disintegration times.

Ethylcellulose is insoluble in water and is used in alcohol solutions. It is available in a range of viscosities, depending upon the degree of substitution of the polymer. Low viscosity grades are typically used in concentrations of 2 to 10% in ethanol (Examples 12 and 13). It may be used for granulating powders which do not readily form compressible granules, such as acetaminophen, acetophenetidin, caffeine, meprobamate and chlorothiazide. Ethylcellulose is also soluble in acetone, methanol, and ethylene dichloride. Tablets prepared from ethylcellulose granulations have relatively short disintegration times without hardening tendencies.

Hydroxypropylmethylcellulose is soluble in water and hydroalcoholic solutions. It is also available in a range of viscosities. It ranks with methylcellulose and PVP as a versatile, nonreactive granulating agent. Like ethylcellulose, it has utility in granulating compressible granules from difficult powders. In most respects it ranks between methylcellulose and ethylcellulose.

Example 12: Ascorbic Acid Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Ascorbic acid, fine powder	250 mg	2.5 kg
Ethylcellulose, 100 cps (as 5% ethanol solution)	45 mg	0.45 kg
Starch	50 mg	0.50 kg
Talc	12 mg	0.12 kg
Stearic acid	5 mg	0.05 kg

Granulate the ascorbic acid with 5% ethylcellulose in ethanol. Pass through a 12 mesh screen, dry at 120° F. Add the stearic acid and pass through a 20 mesh screen; add the starch and talc, mix well, and compress using 13/32-in. standard concave punches.

Example 13: Acetominophen Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Acetaminophen (fine powder)	325 mg	3.25 kg
Ethylcellulose, 100 cps (5% in alcohol)	q.s.	q.s.
Starch	20 mg	200 g
Guar gum	15 mg	150 g
Magnesium stearate	12 mg	120 g

Moisten the acetaminophen with the ethylcellulose in alcohol, and granulate by forcing through a 14 mesh screen. Air-dry the granulation, add the magnesium stearate, and size by passing through an 18 mesh screen. Finally, add the starch and guar gum; mix in a twin shell blender 3 min; then compress using 13/32-in. standard cup punches.

Polyacrylamides are water-soluble polymers also available in a range of viscosities. In 2 to 5% solution they produce granulations similar to those produced with starch paste (Example 14). However, they produce somewhat softer tablets with the disadvantage of having longer disintegration and dissolution times.

Polyvinyloxoazolidones are a group of water-soluble polymers which can be used in 2 to 10% solutions as binding agents. In practice they resemble PVP but with the advantage of being nonhygroscopic. They can be used to granulate a variety of both insoluble and soluble powders. These polymers produce soft but compressible powders with excellent disintegration and dissolution properties. The

Example 14: Penicillin Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Potassium phenoxymethyl penicillin	250 mg	2.5 kg
Calcium carbonate	150 mg	1.5 kg
Lactose (fine powder)	100 mg	1.0 kg
Acrylic polymer, 5% in anhydrous alcohol with 1% stearic acid	q.s.	q.s.
Alginic acid	25 mg	0.25 kg
Sta-Rx 1500 starch	50 mg	0.50 kg
Magnesium stearate	12 mg	0.12 kg

Mix the calcium carbonate and lactose and granulate through a 14 mesh screen after wetting with the alcoholic solution of acrylic polymer and stearic acid; air-dry. Then allow to dry completely in an oven at 140° F. Force through an 18 mesh screen, then mix with the potassium phenoxymethyl penicillin, alginic acid, Sta-Rx, and magnesium stearate. Compress using 1/2-in. flat-face, bevel-edge punches. Calcium carbonate is used to provide an alkaline pH environment.

advantage of these polymers is that they are available in a range of viscosities and they do not greatly interfere with disintegration and dissolution times. Since some are water soluble, and others are soluble in alcohol and ranges of hydroalcoholic solvents, they offer a wide range of applicability and utility. They provide a wide range of nonreactive binders which can be used in aqueous and nonaqueous solvents.

Water or alcohol alone is often sufficient in binding various powders in the granulating liquid, depending upon the physical properties of the powders and the presence of binders in the dry form. Thus powder mixtures containing sugar may be granulated using water or water-alcohol mixtures. Binders such as tragacanth and pregelatinized starch may be added dry and the powder mixture granulated with water. In some cases this may offer advantages such as a softer granulation and shorter disintegration and dissolution times.

C. Lubricants

Lubricants are used in tablet formulations in order to ease the ejection of the tablet from the die, to prevent sticking of the tablets to the punches, and to prevent excess wear on dies and punches. Lubricants should be carefully selected for efficiency in compression and according to the specifications of the final tablet, as many studies have shown that there is no universal lubricant. Two of the factors that are critical to lubricant use are the particle size of the lubricant and the type

and extent of mixing. Lubricants are used to coat the tablet granules, and so the lubricants should be added to the tablet granulation with light mixing. Variation in particle size between different lots of the same lubricant will also affect the properties of the tablet formulation.

The addition of lubricants to granulations may be accomplished in several ways. The lubricant may be added directly to the granulation in a mixer or blender and mixed. This is not an efficient method since the dispersion of the lubricant may not always be complete, or stratification or unblending may occur. Another approach is to remove some fines by screening a portion of a granulation through a 60 mesh screen, mix the lubricant with the fines, and then add the mixture of fines and the lubricant back to the granulation with appropriate mixing. This is an efficient method of incorporating lubricants into a granulation. The wet granulation process offers one approach of lubricant addition which is not feasible with direct compression or dry granulation. In wet granulations of abrasive materials and materials that are difficult to lubricate, it is possible to add certain lubricants dissolved in the granulating solution. Although this is not a common practice, it is an approach which may be useful for the formulator to consider (Example 14).

Lubricants may be broadly divided into two categories: (1) the hydrophobic-type lubricants such as fats and oils, which are the most widely used, and (2) the soluble lubricants, which are used largely for tablets meant to be dissolved by effervescence. The hydrophobic fatty lubricants are the most effective, but excessive use of this type of lubricant will result in rendering the tablet hydrophobic and retarding disintegration of the tablet and drug dissolution. Used in appropriate amounts, and possibly with a surfactant added in the formulation, hydrophobic lubricants do not generally pose problems with their use. A list of the commonly used tablet lubricants is shown in Table 5.

Stearic acid and magnesium and calcium stearate are efficient lubricants but have certain disadvantages. Stearic acid is acidic and should not be used with alkaline salts of organic compounds such as sodium phenobarbital, sodium saccharin, and sodium bicarbonate. With sodium phenobarbital, stearic acid will cause excessive sticking of the tablets on compressions, and form sodium stearate and phenobarbital on standing. Magnesium and calcium stearates are probably the most widely used lubricants in tablet formulations (Example 15). They are available in much smaller particle size than stearic acid, and therefore smaller quantities are

Table 5

Tablet Lubricants

Magnesium stearate	Talc
Calcium stearate	Polyethylene glycol 4000
Zinc stearate	Polyethylene glycol 6000
Hydrogenated vegetable oils	Sodium benzoate
Sterotex	Sodium lauryl sulfate
Polyoxyethylene monostearate	Magnesium lauryl sulate
Light mineral oil	

Example 15: Laxative Tablets (Chewable)

Ingredient	Quantity
Phenolphthaline	64 mg
Powdered sugar 4×	750 mg
Powdered cocoa (defatted)	350 mg
10% Gelatin solution	q.s.
Calcium stearate	12 mg
Talc	60 mg

Mix the phenolphthaline, sugar, and cocoa and moisten with the gelatin solution. Pass through an 8 mesh screen and dry in a tray oven at 120 to 130° F. When dry, reduce granule size by passing through a 16 mesh screen. Mix the calcium stearate and talc, pass through a 100 mesh screen, add to the granulation, and compress to weight using 5/8-in. flat-face punches.

required because of the greater coating properties resulting from the small particle size. Of the two, magnesium stearate is considered the more efficient lubricant and is more widely used. The metallic stearates are alkaline in reaction and, although satisfactory for most tablet formulations, they cannot be used in products containing aspirin, some of the vitamins, and most alkaloidal salts (especially belladonna alkaloids). The water-proofing property imparted to tablets by these lubricants can be counteracted by the use of a surfactant such as sodium lauryl sulfate. The hydrophobic lubricants can also affect tablet hardness, and this effect is particularly critical in the case of direct compression formulations. For this reason, it is important to have adequate control of particle size of the lubricant and the mixing procedure and time for adding the lubricant.

Zinc stearate, because of its lack of reactivity, small particle size, lack of alkalinity, and excellent lubricating properties, has been used in direct compression—especially in granulation blends.

Where alkaline stearates cannot be used, a hydrogenated vegetable oil such as Sterotex can be used.

Example 16: Calcium Phosphate-Vitamin D Tablets

Ingredient	Quantity
Dicalcium phosphate	1.0 g
Sodium chloride	4 mg
Mannitol	150 mg
Starch	260 mg
Ergosterol	1.25 mg (50,000 USP units)

Example 16 (continued)

Ingredient	Quantity
Vanillin	5 mg
Alcohol	25 mg
Sterotex	15 mg
Water	q.s.

Dissolve the ergosterol and vanillin in the alcohol, and mix with 150 mg of the starch. Add this to the mixture of dicalcium phosphate and mannitol. Mix well. Dissolve the salt in water and moisten powders until proper wetness is obtained; then granulate through a 12 mesh screen. Dry in an oven at 120 to 130° F and size through a 16 mesh screen. Mix the Sterotex with the remaining starch and blend into the granulation, mixing for 10 min. Compress to weight using 3/4-in. flat-face punches.

Sterotex is a refined, bleached, and deodorized hydrogenated vegetable oil that is spray-congealed to yield a powder form. While its particle size is not as small as may be desirable, the establishment of appropriate blending times with specific granulations can aid in the distribution of this lubricant on the granules through the attrition of the lubricant powder. Sterotex is soluble in light mineral oil on heating, and this mixture can be used to advantage in that it can be sprayed onto granulations for better distribution. Also, it tends to retard the migration of the mineral oil into the granules. Sterotex is soluble in hexane, and this solution may also be used by spraying onto the granulation in a closed mixer equipped to remove the hexane under reduced pressure.

Other hydrogenated vegetable oils atomized into fine, free-flowing powders (such as Duratex) which are available may also be used as lubricants. An often overlooked, efficient liquid lubricant is light mineral oil having a Saybolt viscosity of 50 to 60 (approximately 8.0 centistokes).

Example 17: Antacid Tablet

Ingredient	Quantity
Calcium carbonate, dense	350 mg
Glycine	150 mg
5% Hydroxyethylcellulose in 50% ethanol	q.s.
Mineral oil, light	3 mg
Starch	30 mg
Talc	5 mg
Methyl salicylate	1.5 mg
Oil of spearmint	0.3 mg

Mix the calcium carbonate and glycine, and add the alcoholic hydroxyethylcellulose solution until sufficiently wet to granulate. Granulate by passing through a 12 mesh screen and air-dry on trays for 4 hr; then dry in an oven at 130 to 140° F overnight. Reduce the granules to a 20 mesh size; mix the oils with the starch and talc; pass through a 100 mesh screen and mix with the granulation. Compress to weight with 13/32-in. standard concave punches.

Because it is a low-viscosity oil, it can be easily dispersed over the granules. Usually 0.5 to 2.0% is adequate. If possible, it should be sprayed onto the particles in a closed mixer, preferably a twin shell blender equipped with an intensifier bar through which the oil is added. On compression, blends lubricated with mineral oil may show mottling, with oil spots on the compressed tablet. This is more noticeable with colored tablets, especially with dark colors. This mottling disappears in a day or two as the oil migrates to the inside of the tablet. One disadvantage of mineral oil as a lubricant is that the blend or granulation must be compressed, in most cases, within 1 or 2 days after addition of the oil. This is due to the fact that the light oil has a tendency to penetrate the granules and lose its effectiveness as a lubricant as it disappears from the surface of the granules. Mineral oil is a largely neglected but excellent lubricant, which greatly reduces die-wall friction and sticking to punches.

A recent development in tablet lubricants in polytetrafluoroethylene, which was first described in a U.S. patent [1]. This lubricant has been reported to be inert and insoluble and to affect the hardness of tablets less than magnesium stearate [2,3]. However, this material is not widely used since its application are largely covered by patent restrictions.

In situations where water-soluble lubricants are required, polyethylene glycol 4000 and polyethylene glycol 6000 have found application.

Example 18: Antacid Tablet (Chewable)

Ingredient	Quantity
Aluminum hydroxide (dried gel)	330 mg
Magnesium hydroxide	85 mg
Mannitol	220 mg
Powdered sugar 6×	110 mg
5% Polyethylene glycol 6000 in 50% ethanol	q.s.
Magnesium stearate	4 mg
Oil of spearment	0.1 mg
Methyl salicylate	1.3 mg

Mix the first four powders well in a sigma-blade mixer and add the alcoholic PEG 6000 solution with mixing until sufficiently wet. Granulate by passing through a 14 mesh screen and dry in an oven at 130 to 140° F or in a fluid bed dryer at 160 to 170° F. When dry, size by forcing through a 16 mesh screen

in an oscillating granulator or through a Fitzmill using a 0 perforated plate. Mix the oils with the magnesium stearate and add to the granulation. Mix for 10 min in a tumble mixer and compress to weight using 1/2-in. flat-face bevel-edge punches.

Example 19: Ephedrine Sulfate-Theophylline-Phenobarbital Tablets

Ingredient	Quantity
Ephedrine sulfate	25 mg
Theophylline	130 mg
Phenobarbital	30 mg
Lactose (fine powder)	90 mg
5% PVP in 50% ethanol	q.s.
Polyethylene glycol 6000	10 mg
Starch	30 mg

Mix the first four powders well and moisten to proper wetness with the alcoholic PVP solution. Granulate through a 14 mesh screen and dry at 130 to 140°F overnight. Mix the polyethylene glycol with the starch, pass through an 80 mesh screen and add to the dry granulation. Mix well. Compress using 5/16-in. standard end punches.

These are materials having molecular weights of 3000 to 3700 and 6000 to 7500, a and melting points of 53 to 56° C and 60 to 63° C, respectively. They may be used with such active ingredients as ascorbic acid, aspirin, thiamine hydrochloride and other water-soluble vitamins. These materials are water-soluble, giving clear solutions when dissolved. As with other lubricants, the smaller the particle size, the greater the distribution on granules and the more efficient the lubricant effect. However, solid polyethylene glycols of extremely small particle size are not commercially available. Particle sizes of 50 μm or less can be attained only by micronization of cooled polyethylene glycol. It has been found that water-soluble tablets can be prepared by direct compression by employing a polyethylene glycol powder of very small particle size (less than 50 μm) as lubricant.

Another soluble lubricant which has found limited use is sodium benzoate. It is slightly alkaline and should not be used with aspirin, iron salts, and some of the vitamins. With iron salts, it forms ferric benzoate which has a pink color and will tend to cause colored mottling of the white tablets. With acidic salts it forms the free acid, and in the presence of moisture in the tablet it tends to crystallize to the surface of the tablet.

Two related water-soluble lubricants are sodium lauryl sulfate and magnesium lauryl sulfate. Both these materials have been found to be essentially similar in lubricant properties, and they are less efficient than the metallic stearates. However, they are soluble lubricants and therefore do not interfere with disintegration or drug dissolution, but rather have been found to improve both

these properties. Since they are alkaline and react readily with acidic materials, they tend to cause softening of tablets containing large proportions of insoluble materials. Dicarboxylic acids, specifically adipic and fumaric acid, have been found useful as lubricants for effervescent tablets.

As a general rule, lubricants should be in as fine a state of subdivision as possible, since the smaller the particle size the greater the efficiency in the granulation. All powdered lubricants should be passed through an 80 or a 100 mesh screen before being added to the granulation. Fine powders such as metallic stearates and silica aerogels can be passed through a 200 mesh screen before use.

D. Disintegrants

Disintegrant is a term applied to substance added to a tablet granulation for the purpose of causing the compressed tablet to break apart when placed into an aqueous environment. The disintegrant in a tablet formula may be considered as a dispersing agent for the dry compacted tablet mass in the gastric milieu. Ideally it should cause the tablet to disrupt not only into the granules from which it was compressed, but also into the powder particles from which the granulation was prepared. The function of the disintegrant is, in effect, to counteract the action of the tablet binder and the physical forces of compression necessary to form the tablet. The stronger the effect of the binder, the more efficient must be the disrupting effect of the disintegrant in order to release the active ingredient in the gastrointestinal tract.

There are two methods used for incorporating disintegrating agents into tab-

Table 6

Disintegrants: Typical Amounts Used

Disintegrant	Concentration in granulation (% w/w)
Starch USP	5 - 20
Sta-Rx	5 - 15
Avicel	5 - 20
Solka-Floc BW 40	5 - 15
Alginic acid	5 - 10
Explotab	5 - 15
Guar gum	5 - 10
Kaolin	5 - 15
Veegum	5 - 15
Bentonite	5 - 15
Acid-base	3 - 20

lets. These methods are called external addition and internal addition. The most common method is the external addition method in which the disintegrant is added to the sized granulation with mixing just prior to compression. In the internal addition method, the disintegrant is mixed with other powders before wetting the powder mixture with the granulating solution. Thus, the disintegrant is incorporated within the granule. When this method is used, part of the disintegrant is added internally and part by external addition. This provides immediate disruption of the tablet into the previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles. Although this latter method is attractive in theory, it is only partially effective in practice—in that any disintegrating agent bound within the granules loses some of its disruptive force because of its encasement by the binder. Nevertheless, where possible, use of the two-step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

Disintegrants comprise a group of materials which, on contact with water: swell, hydrate, change in volume or position, or react chemically to produce disruptive changes within the tablet. This group of materials includes various forms of starches, celluloses, certain algins, vegetable gums, clays, ion-exchange resins and acid-base combinations. A list of commonly used tablet disintegrants is given in Table 6.

Starch is the most widely used and the best established disintegrant. Starches are obtained from various sources such as wheat, corn, rice, and potato. The most widely used material is cornstarch (Example 20). It is available in various grades of whiteness and with various moisture contents ranging from 3 to 12%. Modified starches are also available. A widely used modified starch is Sta-Rx 1500,

Example 20: Acetaminophen Tablets

Ingredient	Quantity per tablet
Acetaminophen	325 mg
Sucrose	60 mg
PVP 10% in alcohol	q.s.
Stearic acid	6 mg
Talc	15 mg
Corn starch	30 mg
Alginic acid	20 mg

Mix the acetaminophen and sucrose and moisten with the alcoholic PVP solution. Pass through a 14 mesh screen to granulate and allow to air dry. When dry, size through a 20 mesh screen, add the cornstarch, talc, and alginic acid, and mix for 10 min in a tumble blender. Next add the stearic acid and allow to mix for 5 min. Compress to weight using 13/32-in. flat-face punches.

which is a compacted or milled starch containing 20% of water-soluble fraction. This material meets all of the USP requirements for starch.

Example 21: Theobromine-Phenobarbital Tablets

Ingredient	Quantity per tablet
Theobromine	325 mg
Phenobarbital	32 mg
Starch	40 mg
10% Acacia solution	q.s.
Sterotex	2 mg
Talc	10 mg
Sta-Rx 1500	15 mg
Solka-Floc BW 40	10 mg

Mix the theobromine, phenobarbital, and starch and granulate with starch paste through a 12 mesh screen. Oven dry at 120 to 130° F and size through an 18 mesh screen. Add the balance of the ingredients, blend for 20 min, and compress using 13/32-in. punches, standard concave.

Sta-Rx can be used both as a binder and a disintegrant when mixed with other dry powders and granulated with water. Furthermore, Sta-Rx is self-lubricating and self-binding and can be used readily in dry granulation or direct compression formulas.

Microcrystalline cellulose is available in two grades, Avicel PH 101 and Avicel PH 102. In the formulation of tablets it can perform as a disintegrant, binder, glidant, or filler—making it an extremely versatile adjunct for the formulator.

Example 22: Meclizine Hydrochloride Tablets

Ingredient	Quantity per tablet
Meclizine hydrochloride	25 mg
Lactose	160 mg
10% Starch paste	q.s.
Avicel	25 mg
Stearic acid	5 mg

Avicel has a fast wicking rate for water. Hence, Avicel and starch make an excellent combination for effecting the rapid disintegration of tablets. The small elastic deformation of Avicel contributes to its disintegration effect. One drawback in the use of Avicel is its tendency to develop static charges with increased moisture content, sometimes causing striation or separation in the granulation. This can be partially overcome by drying the Avicel to remove moisture, since moisture content above 3% tends to produce static charges during mixing and compression. Avicel when compressed dry functions as a disintegrant. Wet granulated, Avicel dried and compressed does not disintegrate as readily as the unwetted. Unlike starch, it cannot be wet granulated without losing some of its disintegrating properties. It can be used with almost all drugs except those which are moisture-sensitive (such as aspirin, penicillins, and vitamins) unless it is dried to a moisture content of less than 2% and then handled only in dehumidified areas.

Solka-Floc is a name applied to several grades of purified wood cellulose. These are designated by BW numbers of which BW 40 is probably the most used. They are white, fibrous, inert, neutral materials which can be used in combination with starch as a disintegrating agent for aspirin, penicillins, and other drugs which are pH- and moisture-sensitive. Its fibrous nature endows it with good wicking properties, and it should be used in combination with starch or some of the clays such as kaolin, bentonite, or Veegum for disintegrating action—especially for tablets having a high content of highly water-soluble drugs (such as ammonium chloride, sodium salicylate, sodium chloride, ascorbic acid, and ferrous gluconate).

Alginic acid is a polymer derived from seaweed comprising D-mannuronic and L-glucuronic acid units. Its affinity for water and high sorption capacity make it an excellent disintegrant. It is insoluble in water, slightly acid in reaction, and it should be used only in acidic or neutral granulations. If used with alkaline salts or salts of organic acids it tends to react to form soluble or insoluble alginates which have gelling properties which increase viscosity and delay disintegration. It may be used in multivitamin tablets, aspirin, and most acid salts of organic bases.

Explotab is sodium starch glycolate, a partially substituted carboxymethyl starch. Explotab granules absorb water rapidly and swell but do not break. The swollen granules remain intact, causing disintegration without bursting and consequent release of the soluble starch fraction—which might cause an increase in viscosity and delay moisture penetration of the tablet. Explotab, like starch, is neutral and inert and, because the granules do not rupture, it is unreactive. It has a lower moisture content than most starches and can be used almost universally as an efficient disintegrant which does not lose its effectiveness with time. It is especially useful with tablets of insoluble drugs such as antacids, barium sulfate, dicalcium phosphate, and meprobamate (Example 23).

Guar gum is a naturally occurring gum which is marketed under the trade-name of Jaguar. It is a free-flowing, completely water-soluble, neutral polymer composed of sugar units and it is approved for food use. It is available in various particle size ranges and finds general use as a disintegrant in tablet formulations. It is not sensitive to pH, moisture content, or solubility of the tablet matrix. Although an excellent disintegrant, it has several drawbacks. It is not always pure white, but sometimes varies in color from off-white to tan. It also tends to discolor with age in alkaline tablets. Therefore, when guar gum is used in uncoated

Example 23: Ferrous Sulfate Tablets

Ingredient	Quantity per tablet
Ferrous sulfate (dried)	300 mg
Corn starch	60 mg
20% Sugar solution	q.s.
Explotab	45 mg
Talc	30 mg
Magnesium stearate	4 mg

Mix the ferrous sulfate and cornstarch; moisten with sugar syrup to granulate through a 12 mesh screen. Dry in a tray oven overnight at 140 to 150° F. Size through an 18 mesh screen, add the Explotab, talc, and magnesium stearate, and compress to weight using 3/8-in. deep cup punches in preparation for sugar-coating.

tablets that are white or of light color, it is necessary to select batches that are white.

Kaolin and bentonite are clays which swell on contact with water. They also have the disadvantage of being off-white in color and varying from batch to batch. They can, however, be used to advantage in tablets of soluble salts or compounds, especially if the tablets are to be coated (to offset the appearance of colored specks from these disintegrants). They are best used in conjunction with other disintegrants such as starch and alginic acid. When wetted in granulations these clays lose their disintegrant properties since they do not swell when rewet.

Veegum is a highly refined isomorphous silicate. It is superior to kaolin or bentonite as a disintegrant and can be obtained as a pure white, amorphous powder. It is slightly alkaline, which fact should be taken into consideration when using Veegum with acidic compounds. Veegum swells to many times its own volume when in contact with water, but loses its disintegrant properties when wetted and dried.

The use of an acid-base mixture consists of adding an organic acid—such as citric, tartaric, or fumaric acid—and sodium bicarbonate or sodium carbonate to the granulation so that, upon contact with water, carbon dioxide is generated, causing disintegration of the tablet by disruption (Example 24). The granulation must be quite dry since any residual moisture may cause the reaction to proceed slowly, liberating CO_2 slowly—with a resulting buildup of pressure if the tablets are tightly sealed in a bottle or other container.

Evaluation of potential new disintegrants is an active area of tablet research as the search for new, improved disintegrants continues. Some of the materials that have been found to have good disintegrating properties continue to be of interest, with efforts to seek application of these materials in tablet formulations, and

Example 24: Magnesium Hydroxide Tablets (Milk of Magnesia Tablets)

Ingredient	Quantity per tablet
Magnesium hydroxide	300 mg
Sugar 6×	60 mg
5% Gelatin solution	q.s.
Magnesium stearate	7 mg
Sodium bicarbonate (fine powder)	30 mg
Citric acid (fine powder)	40 mg
Oil of peppermint	0.5 mg

Mix the magnesium hydroxide and sugar and moisten with the gelatin solution. Pass through a 12 mesh screen and dry at 130 to 140° F. Size by passing through a 16 mesh screen. Add the sodium bicarbonate, citric acid, and oil of peppermint and mix well. Finally add the magnesium stearate, mix in a twin-shell or double-cone mixer for 3 to 5 min, and compress using 7/16-in. flat-face bevel-edge punches.

also to seek appropriate regulatory clearance. Some of the materials that have been found to be excellent disintegrants are CLD, Polyplasdone XL, and a cation exchange resin.

These materials represent a new generation of disintegrants that enable substantially greater reduction in disintegration time than previously achieved with starch and other long-established disintegrants. This property is particularly useful in tablet formulations containing highly water-insoluble drugs in micronized form. It has been found that these materials also exhibit a degree of binding action, enabling substantial improvement in tablet friability when used in relatively low concentrations.

The polymer CLD is a cross-linked sodium carboxymethylcellulose. It is a substantially water-insoluble anionic cellulose derivative that meets all the specifications for sodium carboxymethylcellulose of the Food and Chemical Codex except that it does not give a clear solution. In a study comparing CLD, Explotab, Sta-Rx, and Avicel, Explotab and CLD were found to show better disintegrant properties than Avicel or Sta-Rx, and they were essentially similar to each other when compared using two direct-compression tablet bases (lactose and dicalcium phosphate dihydrate) and a wet granulation formulation (consisting of calcium sulfate granulated with an aqueous PVP solution).

Cation-exchange resin has been investigated as a disintegrant and seems to offer considerable promise for this function. The cation-exchange resin is a potassium salt of a weak acid and is based on a methacrylic acid divinylbenzene copolymer. The disintegrant action of these substances has been examined in systems prepared by both wet granulation and direct compression. The resin was found to be a superior disintegrating agent for a soluble drug (sodium salicylate) and an insoluble drug (phenacetin).

Polyplasdone is a cross-linked polyvinylpyrrolidone. It has been found to be a good disintegrant at levels of 0.5 to 5% for tablets of poorly water-soluble drugs prepared by wet granulation and direct compression.

E. Glidants

Glidants are substances added to cohesive powders and granulations in order to improve their flow properties by reducing interparticle friction. When specifically applied to tableting operations, glidants are added to granulations or powder blends to improve flow in the hopper—and into the die cavities of the tablet press. Those used in tableting include starch, talc, colloidal silicon dioxide, various silicates, metallic stearates, and calcium phosphate.

The effects produced by different glidants depend on: (1) their chemical nature in relation to that of the powder or granule (i.e., on the presence of unsaturated valencies, ionic or hydrogen bonds on their respective surfaces which could interact chemically) and (2) physical factors including the size and shape distribution of particles of both the glidant and other formulation components, moisture content, and temperature. In general, hydrophilic glidants tend to be more effective on hydrophilic powders than on hydrophobic powders, and the opposite occurs with the hydrophobic glidants. For any particular system there is usually an optimum concentration above which the glidant may start to act as an antiglidant [4]. This optimum depends, among other things, on the moisture level in the sample, and it may be related to the glidant's propensity to act as an anticaking agent. Some of the usual glidant materials used and the concentrations required for optimum glidant effect are shown in Table 7.

Table 7

Glidants Used Typically in Tablets

Glidant	Concentration for optimum flow (% w/w)
Starch	2-5
Talc	0.3-10
Magnesium stearate	0.2-2
Calcium stearate	0.25-3
Zinc stearate	0.2-2
Dibasic calcium phosphate	1-3
Magnesium carbonate	0.5-2
Magnesium oxide	0.5-2.5
Calcium silicate	0.5-1
Silica aerogels	0.1-0.5

The silica-type glidants are the most efficient because of their small particle size. They are available as two types, both insoluble: the pyrogenic silicas prepared by the burning of silicon tetrachloride and the precipitated type prepared by the precipitation of soluble silicates. The pyrogenic silicas, as a rule, have smaller particles, which tend to be spheroid in shape. The pyrogenic silicas are available in both hydrophilic and hydrophobic forms. The particle size of various types of silica glidants is shown in Table 8.

There are no specific rules dictating the amount of any glidant required for a particular granulation. Glidants differ not only in chemical properties, but also in their physical characteristics such as size, frictional properties, structure, and density. Therefore the concentration of a glidant varies with the material to which it is added. The kind and concentration of glidant to be added may be evaluated by one of the various methods.

One method is the determination of the angle of repose or repose angle. When powdered granular material is allowed to fall freely from an orifice onto a flat surface, the material deposited forms a cone. The base angle of the cone is referred to as the repose angle. By this method, it has been found, for example, that the repose angle of a sulfathiazole granulation increases with decreasing particle size. Talc added in small quantities reduces the repose angle of the granulation but tends to increase the repose angle at higher concentration, becoming an antiglidant. Addition of fines causes a marked increase in the respose angle and magnesium stearate has little or no effect.

Another method of determining the effects of glidants upon the flow properties of a granulation is that of allowing a given amount of granulation with and without glidant to flow through an orifice ranging in size from 3/8 to 1 in., depending upon the size of the granules, and observing the efflux time. The orifice may be a straight-wall die or it may be funnel-shaped. An example of this method is shown in Table 9. The data of Table 9 may be stated in terms of a glidant efficiency factor f, where

$$f = \frac{\text{rate of flow in presence of glidant}}{\text{rate of flow in absence of glidant}}$$

The particle size of the added glidants becomes important since it is the ability of the additive to coat the surface of the granules that determines its efficiency.

Table 8

Particle Size of Silica Glidants

Material	Particle size (nm)
Pyrogenic silica (Cab-O-Sil)	15
Hydrated sodium silicoaluminate	22
Amorphous nongelled precipitated silica	12
Silica Hydrogel	10×10^3
Silica Hydrogel (exhibiting aerogel-type structure)	3.3×10^3

Table 9

Effect of Silica Aerogel on Flow of Lactose Granulated with Starch Paste

Amount of silica aerogel	Efflux time, 1/2-in. orifice (sec)
0.00	82
0.05	72
0.10	55
0.15	42
0.20	38
2.25	36
0.30	44

Since many materials used as glidants are also efficient lubricants, a reduction of interparticulate friction may be involved. The reduction may take place in two ways. Fine material may adhere to the surface rugosity, which will minimize the mechanical interlocking of the particles. Rugosity refers to a factor to define deviation of a shape from a spherical shape. The coefficient of rugosity is defined as the ratio of the actual surface area (determined by a suitable method) to the geometric surface area (found by microscopy). The added material may also possess a coefficient of friction which is less than that of the granulation and it may therefore decrease interparticulate friction. Certain glidants such as talc and silica aerogels roll up under low shear stresses to produce a "ball bearing" type of action, causing the granules to roll over one another.

Many powders acquire a static charge during handling, in mixing, or in the induced die feeder. The addition of 1% or more of magnesium stearate or PEG 4000, or 2% or more of talc effectively lowers the accumulation of static charge.

Magnesium oxide should be considered as an auxiliary glidant in combination with silica-type glidants, especially for granulations which tend to be hygroscopic or are somewhat high in moisture. Magnesium oxide tends to bind water and keep the granulation dry and free-flowing.

F. Color Additives

The coloring of tablets, in addition to its aesthetic value, serves to distinguish one product from another during product manufacture as a control attribute. It also serves to identify the particular medication to the patient. Pastel shades are generally used as they are less likely to show mottling than darker colors. Colors used in medicinal products are limited to those certified by the Food and Drug Administration as: food, drug, and cosmetic (FD&C) colors; drug and cosmetic (D&C) colors; or external drug and cosmetic (Ext. D&C) colors. Colors which are FD&C or D&C are suitable for internal and external use. These colors are dyes, their lakes, and certain natural and derived colorants. Lakes are dyes adsorbed

generally on aluminum hydroxide; they are typically available as regular (containing 15 to 25% adsorbed dye) or as concentrated (with 32 to 40% adsorbed dye). Lakes are almost completely insoluble in water but may bleed slightly.

Because the Food and Drug Administration determines what colors may be used, and also recommends limits for some of them, the formulator must always be aware of the current applicable regulations. Changes made in the listing or delisting of color additives appear in the Federal Register, which is published every working day. A general guideline for the use of colors is to limit the amount added to a maximum of 0.05% of soluble dyes in any product. Table 10 contains a list of colorants permitted as of March, 1978.

Because they are used in very low concentrations, certified dyes are often treated as inert materials, and their potential chemical reactivity is frequently overlooked. Dyes react with various pharmaceutical excipients. Sugars such as lactose, dextrose, and sucrose increase the rate of fading of FD&C Blue No. 2, while this does not occur with mannitol and sorbitol. Quaternary ammonium compounds such as cetyl pyridinium chloride, benzalkonium chloride, and others react with FD&C Blue No. 1 and D&C Yellow No. 10 to form insoluble complexes.

Table 10

Color Additives FDA Certified as of March, 1978

FD&C Red No. 3 (erythrosine)
FD&C Red No. 40 (Allura red)
FD&C Yellow No. 5 (tartrazine)
FD&C Yellow No. 6 (sunset yellow)
FD&C Blue No. 1 (brilliant blue)
FD&C Blue No. 2 (indigotine)
FD&C Green No. 3 (fast green)
D&C Blue No. 6 (indigo)
D&C Green No. 5 (alizarin cyanine green F)
D&C Green No. 6 (quinizarin green)
D&C Red No. 19 (rhodamine B)
D&C Red No. 22 (eosin YS)
D&C Red No. 33 (acid fuchsin D)
D&C Red No. 37 (rhodamine B stearate)
D&C Yellow No. 10 (quinoline yellow WS)
Ext. D&C Green No. 1 (naphthol green B)
Ext. D&C Orange No.4 (orange II)
Ext. D&C Yellow No. 1 (metanil yellow)

Wet granulation offers a convenient method of incorporating colorants into the granulation by dissolving or dispersing the dye or lake in the binder liquid. This makes for uniform dispersion and color distribution to produce homogeneous granulations and tablets. Soluble dyes dissolved in the binder solution will produce a homogeneous wet mass; but on drying certain soluble dyes have a tendency to migrate to the surface of the granules, producing mottled tablets on compression. This can be overcome by using lake dyes and dispersing them in the binder liquid with the aid of high-speed mixing. If soluble dyes are used they should first be adsorbed on calcium sulfate, tricalcium phosphate, starch, or some other major ingredient. The inclusion of 5 to 10% of microcrystalline cellulose in the powder mix helps prevent the migration of soluble dyes. Migration of dyes is greater if alcohol or hydroalcoholic solutions are used as the solvent for the binder.

A new concept in colorants now on the research horizon is nonabsorbable polymeric food colors. The rationale underlying the development of polymeric dyes stems from the conceptual basis that ingredients that are absorbed intact or metabolized may interact with target organs and tissues, and this may constitute a potential toxic risk, especially over the life span of man. These so-called polydyes are prepared by incorporating stable biological chromophores onto a nondegradable, nonabsorbable polymer chain. Animal studies have shown that these dyes are not absorbed from the intestinal tract and therefore do not constitute a toxicity hazard in the body. Experience thus far indicates the dyes are readily soluble, can be dry-blended, spray-dried, emulsified, and so forth, and may be widely used in foods, beverages, fountain syrups, extracts, and concentrates. Lakes formed from polydyes are unusual from a number of viewpoints. In lake manufacture, the polydyes are virtually instantaneously and quantitatively adsorbed onto alumina. Unlike FD&C dyes, the filtrates from polydye lake slurries are free of unadsorbed dye. Another unusual feature of these lakes is the very high degree of dye loading that can be achieved. Lakes with polydye loadings on alumina in excess of 70% can be readily obtained. This greatly increases the number of lake shades obtainable from any one primary dye or from blends of dyes.

Naturally occurring colorants which have been known and used in the past have recently become of considerable interest. This interest stems from FDA action in delisting certified dyes and the uncertainty of future action on other synthetic colorants. Table 11 lists some of the naturally occurring colorants which are available at the present time in commercial and semicommercial quantities. Various shades of these colors are available under trade names from various suppliers.

G. Flavors and Flavor Modifiers

Flavor influences the acceptability of nearly everything that is tasted, whether it be food, beverage, or medicine. The research pharmacist, in flavoring a new product, must have some basic knowledge of flavors for masking bitter, sour, salty, and other objectionable tastes of drugs, in liquids or in solid dosage forms such as chewable tablets. For example, it is important to know that a top note (predominant first taste) and a back note (complementing subordinate aftertaste) combine to give a rounded fullness of flavor, and for this reason it is usually better to use the proper combination of two flavors rather than only one. The research pharmacist should also know something of flavor enhancers and modifiers as aids in masking objectionable tastes.

Table 11

Some Commercially Available Natural Colors

Colorant	Color	Source
Carmine	Red	Dried female cochineal insects
Grape-skin extract	Purple	Grapes
Riboflavin phosphate	Yellow-Orange	Synthetic
Annatto	Yellow	Extract from seeds of Fixa orellana
Beet juice, dried	Red	Beets
Cranberry juice, dried	Red	Cranberries
Caramel	Brown	Sugar
Turmeric	Yellow	Indian saffron

Sugar syrups, glycerine, and sorbitol impart not only sweetness but also a smooth mouth-feel which in itself aids most flavors. Fructose is approximately 50% sweeter than sucrose, and the use of high-fructose syrups increases both palatability and sweetness.

The cooling sensation produced by menthol produces a refreshing effect, as in chewing gum, mints, and cough drops.

The burning oleoresins of ginger and capsicum produce the lively taste of ginger ale and Tabasco sauce and, judiciously used, can overcome the flat, chalky taste of aluminum and magnesium hydroxides used alone or in conjunction with peppermint or spearmint.

The aldehydes, as a class, elicit a pleasing response. The acetaldehyde of sherry flavor, the cinnamic aldehyde of cassia and cinnamon, the benzaldehyde of cherry and almond flavors, the citral of lemons, and the C-10 and other aldehydes of orange are the top notes of these flavors.

The phenols as a class, including oils of wintergreen and clove and such substances as thymol, eugenol, and vanillin, have a marked numbing action in the mouth. Many other aromatic substances including oils of sassafras, cassia, and bitter almond also have a numbing effect which can be used to mask highly acidic and certain salty tastes, such as mandelic acid and ammonium chloride.

Salt is one of the most important of flavor modifiers. Where excessive sweetness may be necessary, the bland, cloying sweet taste can be overcome by the addition of salt. An example is the use of salt in fudge and taffy.

Chocolate has been found to be the best masking agent for bitter tastes such as quinine, while anise and raspberry are most effective for salty tastes such as ammonium chloride.

Among the fruit flavors in wide use today are grape, black currant, strawberry, lime, tangerine, apricot, peach, banana, and pineapple. In a survey of 200 currently popular proprietary pharmaceuticals of all types, the most frequently occurring flavors (in descending order of frequency) were cherry, fruit oragne, raspberry, chocolate, mint, and anise. Cherry was the choice for antibiotics,

chocolate for sulfa drugs, orange for vitamins, mint for antacids, and mint and anise for cough-cold preparations.

Monosodium glutamate as a flavor modifier has great potential in certain types of pharmaceuticals. The metallic taste of hematinics and the long-lived bitter taste of barbiturates are considerably reduced in intensity and duration. It has been suggested that, rather than overflavoring bad-tasting medicinals with strong aromatics, a careful blending of flavors with other materials such as vanillins, glutamates, salt, and spice oils would better disguise objectionable tastes.

Unpleasant odors of drugs can be overcome with aromatic spices and fixatives. Acacia syrup is an excellent demulcent vehicle for substances having an acrid or burning taste. Citric acid syrup or lemon syrup is good for salty or acidic compounds. Orange syrup is the flavor of choice for acetates, bromides, citrates, salicylates, and most expectorant products.

IV. Direct Compression Tableting

Until the late 1950s the vast majority of tablets produced in the world were manufactured by a process requiring granulation of the powdered constituents prior to tableting. The primary purpose of the granulation step was to produce a free-flowing and compressible mixture of active ingredients and excipients. The availability of new excipients or new forms of old excipients, particularly fillers and binders, and the invention of new (or the modification of old) tablet machinery have allowed the compression of tablets by the much simpler procedure of direct compression. However, in spite of the many obvious advantages of tableting by direct compression, it has not been universally adopted even in those cases where it would seem to be technically feasible and advantageous. The reasons for this can be understood only by reviewing the development of direct compression technology and the decision-making steps involved in selecting one manufacturing process over another.

The term direct compression was long used to identify the compression of a single crystalline compound (usually an inorganic salt such as sodium chloride, sodium bromide, or potassium bromide) into a compact without the addition of any other substances. Few chemicals possess the flow, cohesion, and lubricating properties under pressure to make such compacts possible. If and when compacts are formed, disintegration usually must take place by means of dissolution—which can take a considerable length of time, delaying drug release, and possibly causing physiological problems such as have occurred in potassium chloride tablets. Furthermore, the effective dose of most drugs is so small that this type of direct compression is not practical.

Pellets of potassium bromide are directly compressed for use in infrared spectrophotometry, and disks of pure drug have been directly compressed for studying intrinsic dissolution rates of solids. However, there are few examples today of direct compression as classically defined in the literature.

The term direct compression is now used to define the process by which tablets are compressed directly from powder blends of the active ingredient and suitable excipients (including fillers, disintegrants, and lubricants) which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary. Occasionally

potent drugs will be sprayed out of solution onto one of the excipients. However, if no granulation or agglomeration is involved, the final tableting process can still be called direct compression.

The advent of direct compression was made possible by the commercial availability of directly compressible tablet vehicles which possess both fluidity and compressibility. The first such vehicle was spray-dried lactose, which, although it was subsequently shown to have shortcomings in terms of compressibility and color stability, initiated the "direct compression revolution." Other direct compression fillers were introduced commercially in the 1960s, including: microcrystalline cellulose, the first effective dry binder and filler; Sta-Rx 1500 starch, a compressible starch which maintains its disintegrant properties; Emcompress, a free-flowing dicalcium phosphate; and a number of direct compression sugars. At the same time major advances were made in tablet compression machinery, such as improved positive die feeding and precompression stages which facilitated direct compression tableting. By the beginning of the present decade the excipients and machinery were available to make possible the direct compression of the vast majority of tablets being manufactured.

A comparison of the steps involved in the three general methods for preparing tablets were shown in Table 1. Wet granulation and dry granulation (slugging) are described elsewhere in this chapter. The simplicity of the direct compression process is obvious. However, it is this apparent simplicity which has caused so many initial failures in changing formulations from wet granulation to direct compression. Direct compression should not be conceived as a simplified modification of the granulation process for making tablets. It requires a new and critical approach to the selection of raw materials, flow properties of powder blends, and effects of formulation variables on compressibility. During the wet granulation process the original properties of the raw materials are, to a great extent, completely modified; as a result a new raw material, the granulation, is subject to compression. Many inadequacies in the raw materials are covered up during the granulation step. This is not in direct compression, and therefore the properties of each and every raw material and details of how these materials are blended become extremely critical in the compression stage of tableting. If direct compression is approached as a unique manufacturing process requiring new approaches to excipient selection, blending, and compressibility, then there are few drugs which cannot be directly compressed. If this is not done, failures are very likely to be encountered.

A. Advantages of Direct Compression

Before exploring the specific problems of formulated direct compression blends and selecting raw materials, it is important to consider the advantages of direct compression: (1) economy; (2) elimination of heat and moisture; (3) prime particle dissociation; (4) stability; (5) particle size uniformity.

The most obvious advantage of direct compression is economy. It is safe to say that there would be a relatively minor interest in the process of direct compression tableting if economic savings were not possible. Savings can occur in a number of areas, including reduced processing time and thus reduced labor costs,

fewer manufacturing steps and pieces of equipment, less space, and a lower consumption of power. Two unit processes are common to both wet granulation and direct compression tableting. They are blending and compression. Prior micronization of the drug may be necessary in either process. Although a number of pieces of equipment such as granulators (Fitzmills) and dryers are not needed in preparing tablets by direct compression, there may be a need for greater sophistication in the blending and compressing equipment. However, this is not always the case.

The advantage which is of greatest significance in terms of tablet quality is that of processing without the need for moisture and heat, which is inherent in most wet granulation procedures, and the high compaction pressures involved in the slugging stage of producing tablets from dry granulations. The unnecessary exposure of any drug to moisture and heat can never be justified; it cannot be beneficial and may certainly be detrimental. In addition to the primary problem of stability of the active ingredient, the variabilities encountered in the processing of a granulation can lead to innumerable tableting problems. The viscosity of the granulating solution—which is dependent on its temperature, and sometimes on how long it is has been prepared—can affect the properties of the granules formed, as can the rate of addition. The granulating solution, the type and length of mixing, and the method and rate of wet and dry screening can change the density and particle size of the resulting granules, which can have a major effect on compaction qualities. The drying cycles can lead not only to critical changes in equilibrium moisture content but also to unblending as soluble active ingredients migrate to the surfaces of the drying granules. There is no question that, when more unit processes are incorporated in a production operation, the chances of batch-to-batch variation are compounded.

Probably one of the least recognized advantages of direct compression is the optimization of tablet disintegration, in which each primary drug particle is liberated from the tablet mass and is available for dissolution. The granulation process, wherein small drug particles with a large surface area are "glued" into larger agglomerates, is in direct opposition to the principle of increased surface area for rapid drug dissolution.

Disintegrating agents added prior to wet granulating are known to be less effective than those added just prior to compression. In direct compression all of the disintegrant is able to perform optimally, and when properly formulated, tablets made by direct compression should disintegrate rapidly to the primary particle state. However it is important that sufficient disintegrant be used to separate each drug particle if ideal dissolution is to occur; this may require a higher concentration of disintegration agents. One bioavailability advantage of making tablets by wet granulation has never been fully appreciated. The wetting of hydrophobic drug surfaces during the granulation step and the resulting film of hydrophilic colloid which surrounds each drug particle can certainly speed up the dissolution process providing that each one of the primary drug particles can be liberated from the granule. Unfortunately, this is not as likely to occur in a tablet made from a granulation as in one made by direct compression. Prime particle disintegration in direct compression tablets depends upon the presence of sufficient disintegrating agent and its uniform distribution throughout the tablet matrix. High drug concentrations can lead to cohesive particle bonding during compression with no interjecting layer of binding or disintegrating agent.

Although it is not well documented in the literature, it would seem obvious that fewer chemical stability problems would be encountered in tablets prepared by direct compression as compared to those made by the wet granulation process. The primary cause of instability in tablets is moisture. Moisture plays a significant role not only in drug stability but in the compressibility characteristics of granulations. While some direct compression excipients do contain apparently high levels of moisture, this moisture in most cases is tightly bound either as water of hydration (e.g., lactose monohydrate) or by hydrogen bonding to surfaces (e.g., microcrystalline cellulose) and is not available for chemical degradation. The role of moisture is discussed further under the description of individual excipients.

One other aspect of stability which warrants increasing attention is that of the effect of tablet aging on dissolution rates. Changes in dissolution profiles are less likely to occur in tablets made by direct compression than in those made from granulations. This is extremely important as the official compendium moves toward requiring dissolution specifications in all solid dosage form monographs.

B. Limitations of Direct Compression

On the basis of the distinct advantages listed above, it is difficult to understand why more tablets are not made by the direct compression process. To understand this fully, one must have an appreciation of not only the technology but the economics of the pharmaceutical industry.

The technological limitations revolve mainly about the flow and bonding of particles to form a strong compact, and the speed at which this must be accomplished in an era of ever-increasing production rates.

Active ingredients can be separated into two categories—high-dose and low-dose drugs. It should be technically possible to tablet almost all drugs with low doses (less than 50 mg) by the direct compression process with a proper choice of excipients and tablet equipment. The problems encountered in direct compression of low-dose drugs center around uniform distribution of the drug (blending) and possible unblending during the compression stage. (This will be discussed in Sections C and D under excipients and formulation.) Drugs characterized by high dose, high bulk volume, poor compressibility, and poor fluidity (flow properties) do not lend themselves to direct compression. A typical example would be some of the antacid drugs, such as aluminum and magnesium hydroxide. While it is possible to densify some drugs or formulations by preprocessing, there is some question as to whether the final tableting process could then be called direct compression.

With an increased emphasis on dissolution and bioavailability, many drugs are commonly micronized. Micronization invariably leads to increased interparticulate friction and decreased powder fluidity and may also result in poorer compressibility. Very often a decision has to be made as to whether to granulate a micronized powder—which may result in a longer dissolution time—or to directly compress a slightly larger particle size of the drug. In either case the decision should not be based on in vitro dissolution tests but on in vivo blood level studies.

The choice of excipients for their properties is extremely critical in formulating direct compression tablets. This is most true of the filler-binder which often serves as the matrix around which revolves the success or failure of the formulation. Direct compression filler-binders must possess both compressibility and fluidity. In most cases they are specialty items available from one supplier.

Direct compression excipients often cost more than comparable fillers used in granulations. In addition, there is a need to set functionality specifications on properties such as compressibility and fluidity, as well as on more traditional physical and chemical properties. These specifications must be rigidly adhered to, in order to avoid lot-to-lot variations in raw materials, which can seriously interfere with tableting qualities. The costs of raw materials and raw-material testing are thus higher in direct compression. However, this increased cost is more than offset by the economics described earlier.

Many active ingredients are not compressible in either their crystalline or their amorphous forms. Thus, in choosing a vehicle it is necessary to consider the dilution potential of the major filler-binder (i.e., the proportion of active ingredient that can be compressed into an acceptable compact utilizing that filler). Fillers-binders range from highly compressible materials such as microcrystalline cellulose to substances which have very low dilution capacity such as spray-dried lactose. It is not possible to give specific values for each filler because the dilution capacity depends upon the properties of the drug itself. In some cases it is necessary to employ tablet presses with precompression capabilities to achieve an acceptable compact at a reasonable dilution factor.

Outside of compressibility failures, the area of concern most often mentioned by formulators is that of blending. The granulation process does lock active ingredients into place and, providing the powders are intimately dispersed before granulation and no drying-initiated unblending occurs after wetting, this can be advantageous. Direct compression blends are subject to unblending in postblending handling steps. The lack of moisture in the blends may give rise to static charges which can lead to unblending. Differences in particle size or density between drug and excipient particles may also lead to unblending in the hopper or feed frame of the tablet press.

The problems of unblending can be approached in either of two ways. The traditional approach involves trying to keep particle sizes or densities uniform. Ideally the vehicle itself should incorporate a range of particle sizes corresponding as closely as possible to the particle size of the active ingredients. This range should be relatively narrow and should include a small percentage of both coarse and fine particles to ensure that voids between larger particles of drugs or filler excipients are filled by smaller-size particles. In such an approach microcrystalline cellulose or Sta-Rx 1500 could be used to fill voids between larger excipient particles such as Emdex or Emcompress. Another approach has been suggested by Crooks and Ho who advocate the process of ordered blending [5]. Ordered blending refers to the blending of ingredients in a specific order rather than placing all ingredients in the blender at the same time. The micronized active ingredient is first blended with the largest particle-size excipient material. The active ingredient is physically trapped in indentations and irregularities in the surface of the filler particles or held by van der Waals and electrostatic forces to the extent that unblending during further mixing or vibration is resisted.

One other technical disadvantage of direct compression is the limitation in coloring tablets prepared in this manner. It is possible through the use of highly micropulverized lakes to obtain light pastel-shade tablets. There is no satisfactory method for obtaining tablets of a uniformly deep color.

Outside of the limitations imposed by vehicle and formulation, there are economic and regulatory considerations necessary in making a decision to convert present products or to develop new products utilizing direct compression technology.

It is interesting to note that, except for spray-dried lactose, all direct compression excipients were developed after the 1961 Kefauver-Harris amendment to the F.D. and C. Act which placed very stringent restrictions on dosage forms as well as drug development. There is no question that this has led to a much more conservative approach to product development and formulation. Because of a 3- or 4-year interval between formulation and marketing, many product development chemists hesitate to develop direct compression formulations with unproven excipients. Further complicating this picture is the sampling of experimental direct compression excipients which were never marketed commercially or were subsequently withdrawn, leading to instability in the specialty excipient marketplace. Of equal importance is the number of companies which tried direct compression formulations that failed when placed in full-scale production. In many cases this could be attributed to a failure to appreciate the complexities of the direct compression technology, failure to set adequate specifications on raw materials, and failure of lot-to-lot reproducibility in the chemicals themselves—principally those which make up the majority of the tablet mass (i.e., the filler-binders and active ingredients).

C. Direct Compression Fillers-Binders

The key to success in direct compression formulations is more closely associated with the functional behavior of excipients, particularly the fillers-binders, than is the case with tablets prepared by means of granulation. Without free-flowing and highly compressible fillers-binders with a high degree of lot-to-lot reproducibility, direct compression on a large scale is impossible.

Kanig has listed 14 properties that an ideal direct compression excipient should possess [6]. In many cases these properties are desirable for any tablet excipient regardless of the method of manufacture to be used.

1. The material should have high fluidity or flowability.
2. It should have high compressibility.
3. It should be physiologically inert.
4. It should be compatible with all types of active ingredients.
5. It should not show any physical or chemical change on aging and should be stable to air, moisture, and heat.
6. It should have a high capacity, which is defined as the amount of active ingredients which the diluent can successfully carry in the direct compression technique. The capacity is generally expressed in terms of percentage of noncompressible material or as optimum drug to diluent ratio.
7. It should be colorless and tasteless.
8. It should accept colorants uniformly.
9. It should be relatively inexpensive.
10. It should possess proper mouth-feel, which is defined as the feel or the sensation in the mouth, produced when the material is used in chewable tablets.
11. It should not interfere with the biological availability of active ingredients.
12. It should have a particle size range which should be equivalent to most active ingredients.
13. It should be capable of being reworked, without loss of flow or compressibility.
14. It should have a good pressure-hardness profile.

In addition to these requirements the bulk density of direct compression excipients is critical, as no densification is possible during the granulation process. A compilation of some of the properties of the most widely used direct compression excipients can be found in Table 12. A comparison of the relative compressibility of excipient fillers is shown in Figures 2 and 3. The compression force-hardness

Table 12

Physical Specifications of Direct Compression Fillers

Filler	Moisture	Bulk density (loose) (g ml^{-1})	Particle size
Spray-dried lactose	5.0%[a]	0.68	0.5% on 60[b] 40% on 140 60% on 200
Fast Flo lactose	5.0%[a]	0.70	66% on 140 21% on 200 15% through 200
Anhydrous lactose	0.25-0.5%	--	16% on 60 65% on 60-200 20% through 200
Emdex	7.8-9.2%	0.64	1% on 20 20% max. through 100
Di-Pac	0.4-.75%	0.58	3% max. on 40 75% min. on 100 5% max. through 200
Nu Tab	<1%	0.70	50% min. on 60 10% max. through 120
Microcrystalline cellulose			
Avicel pH 101	<5%	0.32	1% max. on 60 7% through 200
Avicel pH 102	<5%	0.34	8% max. on 60 45% on 200
Sta-Rx 1500 Starch	12%	0.62	2% on 80 25% on 200 50% through 270
Unmilled dicalcium phosphate (Emcompress)	0.5%	0.91	100% through 20 60% through 100

[a] Contains 4.5% water of hydration.
[b] Mesh size of screen.

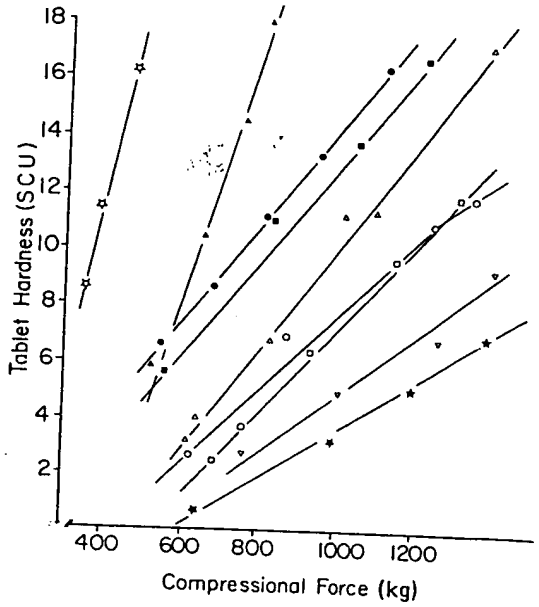

Figure 2. Compressibility of direct compression fillers containing 2% stearic acid. Key: ☆ Avicel; ▲ Celutab; ● Fast Flo lactose; △ anhydrous lactose; ■ Nu Tab; □ Di-Pac; ▽ dicalcium phosphate; ○ spray-dried lactose; ★ Sta-Rx 1500 starch.

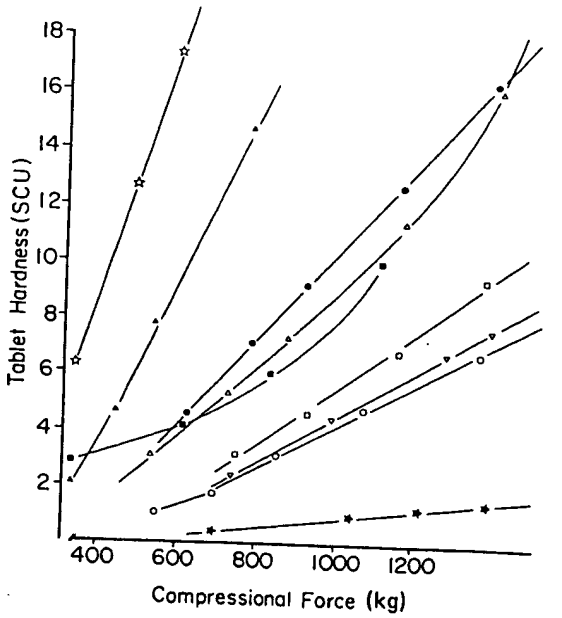

Figure 3. Compressibility of direct compression fillers containing 0.75% magnesium stearate. Key: ☆ Avicel; ▲ Celutab; ● Fast Flo lactose; △ anhydrous lactose; ■ Nu Tab; □ Di-Pac; ▽ dicalcium phosphate; ○ spray-dried lactose; ★ Sta-Rx 1500 starch.

profiles are shown in the presence of two lubricants, 2% stearic acid and 0.75% magnesium stearate. The above-mentioned table and figures are intended to serve as a background for the discussion on individual excipients which follows.

Spray-dried lactose is the earliest and still most widely used direct compression filler. It is one of the few such excipients available from more than a single supplier. In spite of many problems this material revolutionized tableting technology. In the production of spray-dried lactose, lactose is first placed in an aqueous solution which is treated to remove impurities. Partial crystallization is then allowed to occur before spray-drying the slurry. As a result the final product contains a mixture of large crystals of α-lactose monohydrate and spherical aggregates of smaller crystals held together by glass or amorphous material. The fluidity of spray-dried lactose results from the large particle size and intermixing of spherical aggregates. The compressibility is due in large measure to the percentage of amorphous material present and the resulting plastic flow which results under compaction pressure.

When spray-dried lactose was first introduced two major problems existed. The one which received the most attention was that of browning [7]. This browning was due to contaminants in the mother liquid, mainly 5-hydroxyfurfural, which were not removed from the mother liquid before spray-drying. The browning reaction was accelerated in the presence of basic amine drugs and catalyzed by tartrate, citrate, and acetate ions [8]. Although the contaminants are now removed during the manufacturing process in many products, the specter of browning still remains. However, at the present time there appears to be no more danger of browning from spray-dried lactose than from any other form of lactose.

The problem of compressibility of spray-dried lactose is still real and troublesome. As can be seen from Figures 2 and 3, the compressibility of spray-dried lactose is borderline, and furthermore it has relatively poor dilution potential. Spray-dried lactose is an effective direct compression filler when it makes up the major portion of the tablet (more than 80%), but it is not effective in diluting high-dose drugs whose crystalline nature is, in and of itself, not compressible. Furthermore, spray-dried lactose does not lend itself to reworking (i.e., it loses compressibility).

Spray-dried lactose has excellent fluidity, among the best for all direct compression fillers. It contains approximately 5% moisture, but most of this consists of water of hydration. The free surface moisture is less than 0.5% and does not cause significant formulation problems. It is relatively nonhygroscopic. If the water of hydration is removed, spray-dried lactose loses its compressibility. Spray-dried lactose has two other advantages in direct compression. It has a high bulk density—meaning that die fill weight is excellent, and lubricants have relatively minor softening effects on compressibility. This is due to the numerous clean surfaces formed during the compaction process. However, the initial borderline compressibility of spray-dried lactose makes even small softening effects damaging and can lead to formulation failure.

After many abortive attempts to improve on spray-dried lactose, a much more highly compressible product was introduced in the early 1970s. This product, called Fast Flo lactose, consists mainly of spherical aggregates of microcrystals. These microcrystals are α-lactose monohydrate, and they are held together by a higher concentration of glass than is present in regular spray-dried lactose. During the manufacturing process the microcrystals are never allowed to grow, but are agglomerated into spheres by spray-drying. Because it is much more

compressible it has replaced regular spray-dried lactose in many new direct compression formulations.

Because of the spherical nature of the spray-dried aggregates, Fast Flo lactose is highly fluid. It is nonhygroscopic and, as is the case with most spray-dried lactose, contaminants which could lead to browning are removed in the manufacturing process. Tablets made from Fast Flo lactose are 3 to 4 times harder than those made from regular spray-dried lactose at the same compression force.

Although the exact amount of glass in Fast Flo lactose is not stated, it is higher than that in regular spray-dried lactose and is known to be critical. It is possible under certain storage conditions (high humidity) to initiate a reaction which will convert the glass to α-lactose monohydrate crystals. This essentially reduces the compressibility of the Fast Flo lactose to that of regular spray-dried lactose or below. Care should be taken in long-term storage of Fast Flo lactose, and compressibility should be monitored. This general precaution applies to all of the direct compression excipients in the sugar class.

Anhydrous lactose is a free-flowing crystalline lactose with no water of hydration. It is available in a white crystalline form which has good flow properties and is directly compressible. Its compressibility profile (compression force versus hardness) is similar to that of Fast Flo lactose. Anhydrous lactose can be reworked or milled with less loss of compressibility than occurs with other forms of lactose. However, anhydrous lactose already contains a relatively high amount of fines (15 to 30% pass through a 200 mesh screen), so that its fluidity is less than optimal. The use of a glidant such as Cab-O-Sil or Syloid is recommended if high concentrations are included in a formulation.

At high relative humidities anhydrous lactose will pick up moisture, forming the hydrated compound. This is often accompanied by an increase in the size of the tablets if the excipient makes up a large portion of the total tablet weight. At a temperature of 45°C and a relative humidity of 70%, plain anhydrous lactose tablets will increase in size by as much as 15% of their original volume. Much has been made of the fact that anhydrous lactose contains less moisture than regular lactose and thus is a better filler for moisture-sensitive drugs. In fact the surface moisture of the anhydrous and hydrous forms is about the same (0.5%) and the water of hydration does not play a significant role in the decomposition of active ingredients. Anhydrous lactose possesses excellent dissolution properties, certainly as good as, if not better than, α-lactose monohydrate.

Extra-fine crystalline lactose has been suggested as a direct compression filler due to its superior fluidity when compared to regular crystalline lactose USP. However, the material contains no glass form and is not as compressible as spray-dried lactose. It would not appear to have any advantages over other forms of direct compression lactose.

Sucrose has been extensively used in tablets both as a filler, usually in the form of confectioners sugar, and, in the form of a solution (syrup), as a binder in wet granulations. Attempts to directly compress sucrose crystals have never been successful, but various modified sucroses have been introduced into the direct compression marketplace. One of the first such products was Di-Pac, which is a cocrystallization of 97% sucrose and 3% highly modified dextrins. Each Di-Pac granule consists of hundreds of small sucrose crystals "glued" together by the dextrins. These individual crystals can be seen if a granule is placed in water and quickly viewed under a microscope. Di-Pac has good flow properties and needs a glidant only when atmospheric moisture levels are high (greater than 50% relative

humidity). It has excellent color stability on aging, probably the best of all the sugars.

Di-Pac is a product which points up the need for setting meaningful specifications in purchasing raw materials for direct compression. The concentration of moisture is extremely critical in terms of product compressibility. Compressibility increases rapidly in a moisture range of 0.3 to 0.4%, plateaus at a level of 0.4 to 0.5%, and rises again rapidly up to 0.8% when the product begins to cake and lose fluidity. The moisture-compressibility profile of Di-Pac is closely related to the development of monomolecular and multimolecular layers of moisture on both the internal and external surfaces of the sucrose granules—a process which increases hydrogen bonding on compression. The dilution potential of Di-Pac and most other sucroses is only average, ranging from 20 to 35% active ingredients.

While moisture concentration of 0.4% is probably optimal for most pharmaceuticals, material of high moisture content is extremely advantageous when making troches or candy tablets. Interestingly, as moisture levels increase, lubricant requirements decrease. Tablets containing high concentrations of Di-Pac tend to harden slightly (1 to 2 SC units) during the first hours after compression, or when aged at high humidities and then dried. This is typical of most direct compression sucroses or dextroses. Like all direct compression sucroses the primary target products are chewable tablets, particularly where artificial sweeteners are to be avoided.

Nu Tab is a directly compressible sugar consisting of processed sucrose, 4% invert sugar (equimolecular mixture of levulose and dextrose), and 0.1 to 0.2% each of cornstarch and magnesium stearate. The latter ingredients are production adjuncts in the compaction process by which the product is made and are not intended to interject any disintegrant and lubricant activity in a final tablet formulation. Nu Tab has a relatively large particle size distribution which makes for good fluidity but could cause blending problems if cofillers and drugs are not carefully controlled relative to particle size and amounts. In formulations Nu Tab has poor color stability relative to other direct compression sucroses and lactoses.

More recently the manufacturers of Nu Tab have marketed another direct compression sucrose under the name Mannitab. Although the chemical composition of these two products is almost identical, the processing procedures have been changed. Mannitab is reported to give better mouth-feel than other sucroses, but it cannot provide the cooling sensation of mannitol, which has a negative heat of solution.

Sugartab is an agglomerated sucrose product containing from 7 to 10% invert sugar. It has very large particle size, and precision blending of the active ingredients could pose significant problems even under ideal conditions. Sugartab also has a much higher lubricant requirement than other direct compression sucroses, requiring as much as 2 times the amount of magnesium stearate or stearic acid normally needed.

One of the most dramatic modifications of natural raw materials for improving tableting characteristics is directly compressible dextrose formerly marketed under the name Celutab and now available as Emdex. This product is spray-crystallized and consists of 90 to 92% dextrose, 3 to 5% maltose, and the remainder higher glucose saccharides. It is available as both an anhydrous and a hydrous product (9% moisture). Reports indicate that the anhydrous form is slightly more compressible than the monohydrate; but the compressibility of both is excellent, being second only to microcrystalline cellulose when not diluted with drugs or other

excipients. The only disadvantage of the anhydrous form is that it will pick up moisture as the relative humidity increases and can form the monohydrate. The commercially available product is the monohydrate and, as water of hydration does not appear to affect drug stability, it is the most widely used form. At approximately 75% relative humidity both forms of dextrose become quite hygroscopic, particularly if they have been milled or sheared on the surface of a die table. Above 80% relative humidity both products liquefy. Tablets produced from Emdex show an increase in hardness of approximately 2 kg at all levels of initial hardness up to 10 kg. The increase occurs in the first few hours after compression with no further significant hardening on long-term storage under ambient conditions. Hardness increases do not result in significant changes in rates of dissolution.

Emdex possesses the largest particle size of all the common direct compression excipients. Blending problems can occur if blends of other excipients are not used to fill in voids. As mentioned in the general discussion, this filler lends itself to ordered blending, where the micronized drug is first blended with the large particle size Emdex, before other excipients are added to the blender. The micronized drug particles become lodged in the pores on the surfaces of the large spheres and are apparently held in place with sufficient attractive force to prevent dislodging during subsequent blending operations.

Crystalline sorbitol will directly compress and is used as a filler and binder in chewable tablets. It forms a relatively hard compact and has a cool taste and good mouth-feel. Its major disadvantage is its hygroscopic nature. If used in an area with a high relative humidity, crystalline sorbitol will lose its free-flowing character, clump in the feed frame, and cause sticking on the surfaces of the die table.

Mannitol is a naturally occurring sugar alcohol introduced into tableting in 1958, and considered an ideal excipient for chewable tablets because of its smooth mouth-feel and negative heat of solution, which gives a cooling effect. Mannitol is most widely used in the form of a powder which is wet granulated, but it is also available in a granular form which can be used in direct compression. However, its rather large particle size (75% between 16 and 80 mesh) make it difficult to blend with active ingredients, particularly potent drugs. It has been successfully used in the granular form as the basis for breath-freshener tablets.

Starch is one of the most widely used tablet excipients but does not, in its normal state, possess the two properties necessary for making good compacts: compressibility and fluidity. There have been many attempts to modify starch to improve its binding and flow properties. The only modification of starch which has received acceptance in direct compression is Sta-Rx 1500 starch. Sta-Rx 1500 starch is a partially hydrolyzed starch which is relatively free-flowing (compared to starch USP), and which will compress into a compact and still maintain its disintegrant properties. Sta-Rx 1500 starch consists of intact starch grains and ruptured starch grains which have been partially hydrolyzed and subsequently agglomerated. It has an extremely high moisture content (12 to 13%), but there is little indication that this moisture is readily available to accelerate the decomposition of moisture-sensitive drugs.

Although Sta-Rx 1500 starch will readily compact by itself, it does not form hard compacts. Its dilution potential is minimal, and it is not generally used as the filler and binder in direct compression, but as a direct compression filler and disintegrant. The only major advantage of Sta-Rx 1500 is that it retains the disintegrant properties of starch without decreasing the fluidity and compressibility

of the total formulation, as is the case with plain starch. Because Sta-Rx 1500 starch, like all starches, deforms elastically when a compression force is applied, it imparts little strength to compacts. As few clean surfaces are formed during compaction, lubricants, particularly the alkaline stearate lubricants, tend to dramatically soften tablets containing high concentrations of Sta-Rx 1500 starch, and they should be avoided whenever possible in formulating tablets. Lubricants such as stearic acid or hydrogenated vegetable oil are preferred in such formulations.

Starch is made up of two fractions, approximately 25% amylose and 75% amylopectin. Amylose is essentially insoluble in cold water and is directly compressible. As a disintegrating agent it is as good as or better than starch. It is available commercially in Europe under the name Amylose V, but is too expensive for routine use. This product also appear to be very sensitive to alkaline stearate lubricants and is too expensive for routine use in direct compression [9].

The first widespread use of cellulose in tableting occurred in the 1950s when a flocked cellulose product, Solka-Floc, was introduced as a filler disintegrant. Solka-Floc consists of cellulose which has been separated from wood by digestion and formed into sheets which are mechanically processed to separate and break up individual fibers into small pieces—which converts the cellulose into a free-flowing powder. However, this material has poor fluidity and compressibility and is not used as a direct compression excipient.

The most important modification of cellulose for tableting was the isolation of the crystalline portions of the cellulose fiber chain. This product, microcrystalline cellulose, Avicel, was introduced as a direct compression tableting agent in the early 1960s and stands today as the single most important tablet excipient developed in modern times. Although it was developed with no thought of tableting in mind, its properties are not far from optimal.

Microcrystalline cellulose is derived from a special grade of purified alpha wood cellulose by severe acid hydrolysis to remove the amorphous cellulose portions, yielding particles consisting of bundles of needlelike microcrystals. Microcrystalline cellulose for direct compression tableting comes in two grades: PH 101, which was the original product, and PH 102, which is a partially agglomerated product with a larger particle size distribution and slightly better fluidity but with no significant decrease in compressibility.

Microcrystalline cellulose is the most compressible of all the direct compression fillers and has the highest dilution potential. This can be explained by the nature of the microcrystalline particles themselves, which are held together by hydrogen bonds in the same way that a paper sheet or an ice cube is bonded. Hydrogen bonds between hydrogen groups on adjacent cellulose molecules account almost exclusively for the strength and cohesiveness. Under compaction forces, the microcrystalline cellulose particles are deformed plastically—due to the presence of slip planes and dislocations on a microscale, and the deformation of the spray-dried agglomerates on a macroscale. A strong compact is formed due to the extremely large number of clean surfaces brought in contact during the plastic deformation.

Two other factors are important in the ability of a comparatively small amount of microcrystalline cellulose to bind other materials during compaction: the low bulk density of the microcrystalline cellulose and the broad range of particle sizes. An excipient with a low bulk density will exhibit a high dilution potential on a weight basis, and the broad particle size range provides optimum packing density and coverage of other excipient materials.

Microcrystalline cellulose has an extremely low coefficient of friction (both static and dynamic) and therefore has no lubricant requirements itself. However, when more than 20% of drugs or other excipients are added, lubrication is necessary. Microcrystalline cellulose generally withstands lubricant addition without significant softening effects. However, when high concentration (greater than 0.75%) of the alkaline stearate lubricants are used, and blending time is long, tablets containing microcrystalline cellulose will soften. This effect is not as pronounced with Avicel PH 102 as it is with Avicel PH 101.

Because of cost and density considerations, microcrystalline cellulose is generally not used as the only filler in a direct compression tablet but is more often found in concentrations of 10 to 30% as a filler-binder-disintegrant. Although it is not as effective a disintegrant as starch in equivalent concentrations, it can be used as the only disintegrant at levels of 20% or higher and has an additive effect with starch at lower levels. Hard compacts of microcrystalline cellulose disintegrate rapidly due to the rapid passage of water into the compact and the instantaneous rupture of hydroxyl bonds. The fluidity of microcrystalline cellulose is poor compared to that of most other direct compression fillers because of its relatively small particle size. However, comparisons based on a weight per unit time flow through an orifice are misleading due to its inherently low bulk density. Small amounts of glidant are recommended in many formulations.

Tablets made from higher concentrations of microcrystalline cellulose soften on exposure to high humidities due to moisture pickup and loosening of interparticulate hydrogen bonds. This softening is often reversible when tablets are removed from the humid environment. Cycling of temperature and moisture over a period of time can cause both increases or decreases of equilibrium hardness, depending upon the total formulation.

Because microcrystalline cellulose is highly compressible, self-lubricating, and a disintegrant, attempts have been made to use it as the only filler-binder in drugs with low dose. It has been found that formulations containing more than 80% microcrystalline cellulose may slow down the dissolution rates of active ingredients having low water-solubility. Apparently the small particles get trapped between the deformed microcrystalline cellulose particles and delay wetting and dissolution. This phenomenon can be easily overcome by adding portions of water-soluble direct compression excipients.

Another form of cellulose advocated for direct compression is microfine cellulose, Elcema. This material is a mechanically produced cellulose powder which also comes in a granular grade (G-250) which is the only form that possesses sufficient fluidity to be used in direct compression. Microfine cellulose is a compressible, self-disintegrating antiadherent form of cellulose which can be made into hard compacts. However, unlike microcrystalline cellulose, it possesses poor dilution potential, losing its compressibility rapidly in the presence of noncompressible drugs. It is not a particuarly effective dry binder due to the large particle size of the G-250 granules and the resistance to fracture under compression. Microfine cellulose forms new fresh or clean surfaces during compression because of the lack of slip planes and dislocations in the cellulose granules. Thus little interparticulate binding occurs, and surfaces "contaminated" by lubricant during mixing show little inclination to form firm compacts.

The only widely used inorganic direct compression filler is unmilled dicalcium phosphate. This material is available in a special particle size range which is ideal for direct compression tableting under the name Emcompress. Dicalcium

phosphate is relatively inexpensive and possesses a high degree of physical and chemical stability. It is nonhygroscopic at a relative humidity of up to 80%. Dicalcium phosphate also resists the loss of water of crystallization when exposed to elevated temperatures. However it does exhibit one anomaly in regard to stability; it will lose water of hydration at elevated temperatures in the presence of high humidities [10]. It is theorized that, at low humidities and high temperatures, the outer surfaces lose water of hydration, causing a surface case hardening which prevents further moisture loss. In the case of high humidities, this case hardening does not occur, and loss of water of hydration occurs from the entire crystalline structure. In combination with microcrystalline cellulose, tablets in a closed container exposed to high temperatures have been found to soften. This is due to loss of the water of hydration—which is picked up by the microcrystalline cellulose, weakening interparticulate bonding.

The fluidity of dicalcium phosphate is good, and glidants are generally not necessary. While it is not as compressible as microcrystalline cellulose and some sugars (Fast Flo lactose, Emdex), it is more compressible than spray-dried lactose and compressible starch. It apparently fractures well under compression, forming clean bonding surfaces. Lubricants exert little softening effect on compacts.

Because it is relatively water-insoluble, tablets containing 50% or more of dicalcium phosphate disintegrate rapidly. Dicalcium phosphate does dissolve in an acidic medium, but it is practically insoluble in a neutral or alkaline medium. Therefore, it is not recommended for use in high concentrations in combination with drugs of low water-solubility. This is of particular concern in formulating tablets which may be used in geriatric patients where the incidence of achlorhydria is significant.

Dicalcium phosphate dihydrate is slightly alkaline with a pH of 7.0 to 7.3, which precludes its use with active ingredients that are sensitive to even minimal amounts of alkalinity.

D. Factors in Formulation Development

More than in any other type of tablets, successful formulations of direct compression tablets depend upon careful consideration of excipient properties and optimization of the compressibility, fluidity, and lubricability of powder blends. The importance of standardizing the functional properties of the component raw materials and the blending parameters cannot be overstressed. Preformulation studies are almost essential in direct compression tableting.

1. Compressibility

Formulation should be directed at optimizing tablet hardness without applying excessive compression force, while at the same time assuring rapid tablet disintegration and drug dissolution. In those cases where the drug makes up a relatively minor proportion of the tablet, this is usually no problem, and concern revolves around homogeneous drug distribution and content uniformity. Often much simpler excipient systems can be utilized, and factors such as relative excipient costs become more important. In those cases where the drug makes up the greater part of the final tablet weight, the functional properties of the active ingredient and the type and concentration of the excipient dominate the problem.

Often the decision revolves about the question of what is the least amount of excipient necessary to form an acceptable and physically stable compact. In regard to the active ingredient it is important to determine: the effect of particle size on compressibility; the effect of form (crystalline or amorphous) on compressibility; possible granulation of the active ingredient by slugging to improve compressibility and increase density.

The most effective dry binder is microcrystalline cellulose. It can add significant hardness to compacts at levels as low as 3 to 5%. It should always be considered first if the major problem in the formulation is tablet hardness or friability. It has been used at levels as high as 65% to bind active ingredients with extremely poor compressibility characteristics. No other direct compression excipient acts as well as a dry binder in low concentrations. The compressibilities of varying fillers have been discussed as they relate to individual substances. Most disintegrating agents (such as starch) or glidants have negative effects on compressibility, although compressible starch is better than plain corn starch.

It might be expected that compressibility properties would be additive: i.e., that a mixture of microcrystalline cellulose and spray-dried lactose would have a compressibility profile some proportionate value between those of the individual ingredients. For instance, Lerk et al. [11] showed an additive effect between most lactose fillers when they were combined with other lactoses or microcrystalline cellulose. However an antagonistic behavior was demonstrated by blends of fast-dissolving vehicles such as dextrose or sucrose with cellulose or starch products. For instance, almost all combinations of microcrystalline cellulose and compressible dextrose gave poorer compressibility profiles and longer disintegration times than either ingredient alone. Bavitz and Schwartz [12] showed essentially additive effects in hardness when blending fillers, but their work did not include either sucrose or dextrose.

2. Fluidity

The fluidity of tablet blends is important not only from the direct effect on uniformity of die fill and thus uniformity of tablet weight, but also from the role it plays in blending and powder homogeneity. Because of the overall smaller particle size encountered in direct compression blends, fluidity is a much more serious problem than in the case of granulations. Comparative flow values of some direct compression excipients have been reported by Ho et al. [13].

It is important that fluidity specifications be placed on all substances, active ingredients, and fillers which make up more than 5% of a final tablet formulation. Fluidity of active ingredients becomes a factor when the drug has been micronized to improve dissolution rate or provide more key particles of drug per tablet. If the amount of drug is small, this problem can be overcome by a proper choice of excipient fillers. However, when the drug makes up higher proportions of the tablet weight, the use of glidants, in addition to careful selection of tablet fillers, is necessary. The most effective glidants are the micronized silicas such as Cab-O-Sil and Syloid. They are generally used in concentrations of 0.1 to 0.5%. At higher levels the weight variation of tablets will often increase, and tablet hardness per specific die volume fill becomes less. Higher concentrations may be helpful as antiadherents and may reduce filming and picking problems on punch faces.

Most direct compression fillers are purposely designed to give good flow properties. In most cases fluidity in terms of <u>volume</u> (not weight) flow per unit time is directly related to particle size. The two fillers with poorest flow

characteristics are microcrystalline cellulose and compressible starch. In the case of the former, two grades are available with PH 102 having better flow properties than PH 101. Almost all disintegrating agents retard fluidity due to particle size. In order to have optimal disintegration into primary particles it is desirable to have the particle size of the disintegrating agent as small as possible, preferably smaller than that of the active ingredient. Because disintegrating agents are generally used in low concentration, this may or may not be a problem. It is possible that some of the new-generation disintegrating agents such as Explotab, CLD cellulose, Polyplasdone XL (as described earlier in the chapter), and Ac-Di-Sol will be particularly advantageous in direct compression formulations as they can be used at lower concentrations.

Highly fluid powder blends facilitate unblending. The narrower the particle size range of all components and the more alike the particle densities, the less chance for unblending or segregation. It is important to note that it is the particle density and not the bulk density that is important in segregation. Cellulose and starch products tend to have lower true densities than sugars or inorganic chemicals. However, the small and angular particle shape of microcrystalline cellulose makes it difficult for higher-density particles to sift down through the spaces between the blend of materials. Major problems with segregation can occur in spherically shaped fillers, particularly if the particle is large and spherical, such as is the case with compressible dextrose and sucrose. In such cases it is necessary to select other excipients to fill the empty spaces, or to purposely preblend a micronized active ingredient with the large-particle filler. This approach is recommended by Crooks and Ho [5], who blended alphaphenazole (mean particle diameter of 2 μm) with coarse direct compression tablet fillers, and then studied the blends, using a sampling method and electron microscopy. After mixing with a 180 to 250 μm size fraction of direct compression sucrose (Di-Pac) for 100 min, the standard deviation of 200-mg samples containing 4 mg of sulfaphenazole was equivalent to that predicted for a random mix. The mix did not appear to segregate during mixing or vibration. It is theorized that blending of the filler particles first (with lubricant, etc.) or simply blending all materials at once would have interfered with the surface attraction of drug particles to filler and resulted in decreased homogeneity.

The trend toward higher tablet-machine output has necessitated the development of more sophisticated feeders because in older designs the dwell time of the die cavity in contact with the feeder was no longer adequate to allow uniform filling. This problem can become even more critical in direct compression because of the smaller mean particle size of direct compression powder. There are two basic approaches to increasing die feeding efficiency: (1) to force material into the die cavity; (2) to improve flow properties of material directly above the die cavity so that the material will naturally flow downward. The latter approach appears to be the more realistic and serves as the basis for most tablet machine modifications for improvement of die fill. One such system, designed by the Manesty Corporation, employs a rotary feeder with two horizontal paddles, which rotate in opposite directions. The paddle speeds can be synchronized with the main drive. It is possible that the use of such positive die feeding equipment may be necessary if optimum fluidity cannot be obtained through careful selection of ingredients and their concentrations.

As direct compression blends may not possess ideal compressibility, operational problems may be reduced by the use of one or two precompression stages which apply compression force in stages, allowing for the escape of entrapped air and the partial relaxation of elastic deformation.

3. Lubrication

Lubrication has always been one of the most complicated and frustrating aspects of tablet formulation. The lubrication of direct compression powder blends is, if anything, more complicated than that of classical granulating. In general the problems associated with lubricating direct compression blends can be divided into two categories: (1) the type and amount needed to produce adequate lubrication; (2) the softening effects which result from lubrication.

Because the overall mean particle size of direct compression blends is less than that for granulations, higher concentrations of lubricants are often needed. The recognized need for small particle size of lubricants in granulations is of even greater importance in direct compression.

Because there are already many more surfaces covered with lubricant in direct compression blends, the softening effect upon compression is magnified. This is particularly true in direct compression fillers which exhibit almost no fracture or plastic flow on compression. Even when all surfaces of a granulation are covered by a layer of lubricant, significant clean surfaces are formed during compression. In most instances standard blending times will result in complete coverage of these surfaces. The same blending times in direct compression blends may or may not cover all primary surfaces. Thus length of blending becomes much more critical in direct compression than in preparation of tablets granulation. If blended long enough, alkaline stearate lubricants will shear off and completely cover all exposed particle surfaces. It may be necessary to avoid the alkaline stearate lubricants completely in some direct compression formulations. The influence of the duration of lubricant and excipient mixing on the processing characteristics of powders—and on the properties of compacts prepared by direct compression—was studied by Shah and Mlodozeniec [14]. They found that ejection force, hardness, disintegration, and dissolution of directly compressed tablets of lactose and microcrystalline cellulose were all significantly affected by blending times. Lubrication of direct compression formulations is one of the more complex and difficult problems faced by a pharmaceutical formulator.

4. Summary

Direct compression tableting should not be considered an easy or simple process but rather an alternative method of making tablets, which should have cost and stability advantages. The physicochemical properties of individual ingredients such as particle size, fluidity, and moisture are most likely to be more critical in tablets prepared by direct compression than in those prepared from granulations. With proper consideration of excipients and equipment there are relatively few drugs that cannot be directly compressed.

E. Formulations for Direct Compression

As indicated above, the development of formulations for direct compression is both an art and a science. In those cases where the active ingredient makes up the greater part of the tablet matrix, emphasis is placed on blending and powder homogeneity. However, in many cases the active ingredient makes up a much greater proportion of the tablet mass, and selection of such ingredients as fillers, lubricants, and glidants is much more critical. Following is a collection of typical

formulations taken from the literature [15]. They illustrate many of the points discussed in Section IV.D.

Example 25: Acetaminophen Tablets USP

Ingredient	Composition (%)	Quantity per tablet (mg)
Acetaminophen USP (granular or large crystal)[a]	70.000	325.00
Avicel PH 101	29.645	138.35
Stearic acid (fine powder)	0.355	1.65
	100.000	465.00

[a]If smaller crystalline size acetaminophen is desired to improve dissolution, it would be necessary to use a higher proportion of Avicel, to use PH 102 in place of PH 101, and to use a glidant. All lubricants should be screened before adding to blender.

Blend the acetaminophen and Avicel PH 101 for 25 min. Screen in the stearic acid and blend for an additional 5 min. Compress tablets using 7/16-in. standard concave or flat bevel tooling.

Example 26: Analgesic Tablets

Ingredient	Composition (%)	Quantity per tablet (mg)
Aspirin USP	33.44	194.00
Salicylamide NF	16.72	97.00
Acetaminophen NF (large crystals or granular)	16.72	97.00
Caffeine USP (granular)	5.60	32.50
Avicel PH 101	25.00	145.00
Stearic acid (powder)	2.00	11.50
Cab-O-Sil	0.52	3.00
	100.00	580.00

Blend all the ingredients, except the stearic acid, for 25 min. Screen in the stearic acid and blend for an additional 5 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 27: APC Tablets (Aspirin, Phenacetin, and Caffeine)

Ingredient	Composition (%)	Quantity per tablet (mg)
Aspirin USP (40 mesh)	44.25	227.00
Phenacetin (60-80 mesh)	31.55	162.00
Caffeine, anhydrous USP	6.35	32.50
Avicel PH 101	16.35	84.00
Stearic acid (powder)	1.00	5.00
Cab-O-Sil	0.50	2.50
	100.00	513.00

Screen the caffeine to remove lumps. Blend all the ingredients, except the stearic acid, for 25 min. Screen in the stearic acid and blend for an additional 5 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 28: Chewable Ascorbic Acid Tablets (100 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
Ascorbic acid USP (Merck fine crystal)	12.26	27.60
Sodium ascorbate USP	36.26	81.60
Avicel PH 101	17.12	38.50
Sodium saccharin (powder)	0.56	1.25
Di-Pac	29.30	66.00
Stearic acid (fine powder)	2.50	5.60
Imitation orange juice flavor	1.00	2.25
FD&C Yellow No. 6 dye	0.50	1.10
Cab-O-Sil	0.50	1.10
	100.00	225.00

Note: It is not possible to make chewable ascorbic acid tablets with over 50% active ingredient. Other direct compression sugars such as Emdex could be used to replace Di-Pac. Magnesium stearate should be avoided in ascorbic acid formulations. Addition of a higher concentration of Avicel will not usually increase tablet hardness.

Blend all ingredients, except the stearic acid, for 25 min. Screen in the stearic acid and blend for an additional 5 min. Compress into tablets using 3/8-in. standard concave tooling..

Example 29: Chewable Ascorbic Acid Tablets (250 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
Ascorbic acid USP (fine crystal or fine granular)	12.09	72.58
Sodium ascorbate USP (crystal or granular)	36.26	217.52
Imitation orange juice flavor	0.70	4.20
Saccharin sodium USP	0.20	0.20
Avicel PH 101	16.80	100.80
Di-Pac	30.00	180.00
Stearic acid	2.50	15.00
Magnesium stearate	0.50	3.00
FD&C Yellow No. 6 lake dye	0.50	3.00
Pyrogenic silica	0.45	2.70
	100.00	600.00

Weigh all materials. Blend in a P-K blender (no intensifier bar) 30 min without lubricants, then 5 min with lubricants. Compress using 7/16-in. standard concave tooling.

Example 30: Ascorbic Acid Tablets USP (250 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
Ascorbic acid USP (fine crystal or granular)	60.0	250.0
Avicel PH 101	20.0	84.0
Sta-Rx 1500 starch	17.5	75.5
Stearic acid (powder) or Sterotex	2.0	8.5
Cab-O-Sil	0.5	2.0
	100.0	418.0

Note: It is important to use free-flowing types of ascorbic acid due to the high concentration in the formulation. Ascorbic acid concentration could be increased slightly by using more Avicel and less Sta-Rx 1500 starch.

Blend all the ingredients, except the stearic acid or Sterotex, for 25 min. Screen in the stearic acid or Sterotex and blend for an additional 5 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 31: Aspirin Tablets USP (5 grain)

Ingredient	Composition (%)	Quantity per tablet (mg)
Aspirin (40 mesh)	80.0	325.0
Avicel PH 101	12.0	48.0
Corn starch	8.0	32.0
	100.0	405.0

Note: Hardness of finished tablets can be improved slightly by replacing corn starch with Sta-Rx 1500 starch with no resultant decrease in disintegration. Use of stearic acid is optional depending on aspirin type and concentration of Avicel.

Blend all the ingredients, except the stearic acid, for 25 min. Screen in the stearic acid and blend for an additional 5 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 32: Aspirin-Caffeine Tablets

Ingredient	Composition (%)	Quantity per tablet (mg)
Aspirin USP (40 mesh crystal)	80.00	384.00
Caffeine	3.30	15.84
Avicel PH 101	10.00	48.00
Corn starch USP	5.95	28.56
Stearic acid	0.75	3.60

Weigh and blend all ingredients in a P-K blender for 20 min. Compress into tablets using 7/16-in. standard concave tooling.

Example 33: Vitamin B_1 Tablets (100 mg; Thiamine Hydrochloride USP)

Ingredient	Composition (%)	Quantity per tablet (mg)
Thiamine hydrochloride USP	30.0	100.00
Avicel PH 102	25.0	83.35
Lactose, anhydrous	42.5	141.65
Magnesium stearate	2.0	6.65
Cab-O-Sil	0.5	1.65
	100.0	333.30

Note: Anhydrous lactose could be replaced with Fast Flo lactose with no loss in tablet quality. This would reduce the need for a glidant (which is probably present in too high a concentration in most of these formulations). Usually only 0.25% is necessary to optimize fluidity.

Blend all ingredients, except the magnesium stearate, for 25 min. Screen in the magnesium stearate and blend for an additional 5 min. Compress using 13/32-in. standard concave tooling.

Example 34: "Maintenance" Multivitamin Tablets

Ingredient	Label claim	Quantity per tablet (mg)	Overage (%)
(1) Vitamin A acetate (dry form 500 IU A and 500 IU D_2 per mg)	5,000 IU A 500 IU D	11.0	10
(2) Thiamine mononitrate USP	1.5 mg	1.65	10
(3) Riboflavin USP 2.0	2.0 mg	2.20	10
(4) Pyridoxine HCl USP	2.0 mg	2.10	5
(5) Stabicote (1% cyanocobalamin in gelatin)	2.0 μg	0.22	10
(6) D-Calcium pantothenate USP	5.0 mg	7.50	50
(7) Ascorbic acid USP (fine crystals)	60.0 mg	66.00	10

Example 34 (continued)

Ingredient	Label claim	Quantity per tablet (mg)	Overage (%)
(8) Niacinamide	20.0 mg	22.00	10
(9) Emcompress or Ditab		26.23	
(10) Avicel PH 101		50.00	
(11) Talc USP		6.00	
(12) Stearic acid (powdered)		3.00	
(13) Magnesium stearate (powdered)		2.00	

Note: This formulation could be converted into a chewable tablet by adding 40 to 50% sugar filler (i.e., Di-Pac and a small quantity of saccharin).

Blend all ingredients in a precision blender. Compress at a tablet weight of 200.0 mg, using 3/8-in. standard concave tooling.

Example 35: Vitamin E Tablet (200 IU)

Ingredient	Composition (%)	Quantity per tablet (mg)
Vitamin E acetate (dry, 50% granular)	80.0	400
Syloid 74	1.0	5
Avicel PH 102	19.0	95
	100.0	500

Weigh all ingredients. Blend ingredients for 15 min in a P-K blender. Compress using 7/16-in. standard concave tooling.

Example 36: Penicillin V Potassium USP Tablets (250 mg; 400 IU)

Ingredient	Composition (%)	Quantity per tablet (mg)
Penicillin V potassium USP (tablet)	50.00	250.00
Avicel PH 102	24.25	121.25
Dicalcium phosphate, anhydrous	22.00	110.00
Magnesium stearate	3.75	18.75
	100.00	500.00

Blend the penicillin V potassium, Avicel PH 102, and dicalcium phosphate for 25 min. Screen in the magnesium stearate and blend for an additional 5 min. Compress using 7/16-in. standard concave tooling.

Example 37: Quinidine Sulfate Tablets USP (200 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
Quinidine sulfate USP	55.85	200.0
Avicel PH 102	40.25	144.0
Cab-O-Sil	0.50	1.8
Stearic acid, powder	2.50	9.0
Magnesium stearate	0.90	3.2
	100.00	358.0

Blend the quinidine sulfate, Avicel PH 102, and Cab-O-Sil for 25 min. Screen in the stearic acid and magnesium stearate and blend for 5 min more. Compress using 3/8-in. standard concave tooling.

Example 38: Phenobarbital Tablets (30 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
Phenobarbital	23	30.59
Avicel PH 101	23	30.59
Spray-dried lactose	52	69.16

Example 38 (continued)

Ingredient	Composition (%)	Quantity per tablet (mg)
Quso F-22	1	1.33
Stearic acid	1	1.33
	100	133.00

Screen phenobarbital to remove lumps and blend with the Avicel. Add spray-dried lactose and blend. Add Quso F-22 and stearic acid and blend until homogeneous mixture is obtained. Compress using 9/32-in. shallow concave tooling.

Example 39: Chlorpromazine Tablets USP (100 mg)

Ingredient	Composition (%)	Quantity per tablet (mg)
Chlorpromazine hydrochloride USP	28.0	100.00
Avicel PH 102	35.0	125.00
Dicalcium phosphate (unmilled) or Emcompress	35.0	125.00
Cab-O-Sil	0.5	1.74
Magnesium stearate	1.5	5.25
	100.0	357.00

Blend all the ingredients, except the magnesium stearate, for 25 min. Screen in the magnesium stearate and blend for an additional 5 min. Compress into tablets using 11/32-in. tooling.

Example 40: Isosorbide Dinitrate Tablets (10 mg, oral)

Ingredient	Composition (%)	Quantity per tablet (mg)
Isosorbide dinitrate (25% in lactose)	20.00	40.00
Avicel PH 102	19.80	39.60

Example 40 (continued)

Ingredient	Composition (%)	Quantity per tablet (mg)
Fast Flo lactose	59.45	118.90
Magnesium stearate	0.75	1.50

Weigh all ingredients. Blend for 30 min in a P-K blender. Compress into tablets using 5/16-in. standard concave tooling.

V. Dry Granulation

Dry granulation refers to the granulation of a powder mixture by compression and without the use of heat and solvent. On a relative basis, it is the least desirable of all the methods of preparing tablet granulations. However, when direct compression is not possible due to the properties and dose of the drug, and wet granulation cannot be used because the drug is sensitive to moisture and heat, then dry granulation remains the only method available. For example, this method has been useful in the granulation of aspirin and of effervescent products. The basic procedure is to form a compact of the material by compression and then to mill the compact to obtain a granulation. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is precompressed on a heavy-duty tablet press, and the resulting tablets or slugs are milled to yield the granulation. The other method is to precompress the powder with pressure rolls using a machine such as the Chilsonator or the Hutt compactor.

The advantages of dry granulation or slugging are that it uses less equipment and space. It eliminates the need for binder solutions, heavy mixing equipment, and the costly and time-consuming drying step required for wet granulation. Slugging can be used to advantage in the following situations:

1. For moisture-sensitive materials (Example 41)
2. For heat-sensitive materials (Example 42)
3. For improved disintegration since powder particles are not bonded together by a binder (Example 43)
4. For improved solubility, as with anhydrous soluble materials that tend to set when wet (Example 44)
5. For improved blending, since there is no migration of active ingredients as might occur during the drying of a wet granulation (Examples 45 and 46)

Some of the disadvantages of slugging are as follows:

1. It requires a specialized heavy-duty tablet press to form the slug.
2. It does not permit uniform color distribution as can be achieved with wet granulation, where the dye can be incorporated into the binder liquid.
3. A pressure roll press such as the Chilsonator cannot be used with insoluble drugs since this may retard the dissolution rate.
4. The process tends to create more dust than wet granulation, increasing the potential for cross-contamination.

Example 41: Aspirin Tablets (5 Grain)

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Aspirin (20 mesh)	325.0 mg	3.250 kg
Starch USP (dried)	32.5 mg	0.325 kg
Cab-O-Sil	0.1 mg	0.010 kg

Note: All operations should be carried out in a dehumidified area at a relative humidity less than 30% at 70° F.

Combine the aspirin, starch, and Cab-O-Sil and mix in a P-K twin-shell blender for 10 min. Compress into slugs using 1-in. flat-face punches. Reduce the slugs to granulation by passing through a 16 mesh screen in a Stokes Oscillating Granulator or through a Fitzpatrick Mill with a #2B screen, medium speed, knives forward. Transfer the granulation to a tablet machine hopper and compress into tablets using 13/32-in. standard concave punches.

Example 42: Effervescent Aspirin Tablets (5 Grain)

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Sodium bicarbonate (fine granular)	2.050 g	20.500 kg
Citric acid (fine granular)	0.520 g	5.200 kg
Fumaric acid (fine granular)	0.305 g	3.050 kg
Aspirin (20 mesh, granular)	0.325 g	3.250 kg

Note: All operations should be carried out in a dehumidified area at a relative humidity less than 30% at 70° F.

Mix the above ingredients in a P-K twin-shell blender for 20 min; transfer to a tablet machine equipped with 1 1/4-in. flat-face punches, and compress slugs approximately 3/8-in. thick. Grind the slugs to a 16 mesh screen. Mix for 5 min in a twin-shell blender and compress into tablets using 7/8-in. flat-face bevel-edge punches.

Example 43: Antacid Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Aluminum hydroxide (dried gel) USP	240.0 mg	2.4 kg
Magnesium hydroxide NF	60.0 mg	0.6 kg

Example 43 (continued)

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Magnesium carbonate NF	60.0 mg	0.6 kg
Sucrose (fine powder 6×)	50.0 mg	0.5 kg
Sta-Rx starch	30.0 mg	0.3 kg
Polyethylene glycol 6000	30.0 mg	0.3 kg
Magnesium stearate	0.5 mg	0.005 kg
Oil of spearmint (spray-dried)	6.0 mg	0.060 kg
Methylsalicylate (spray-dried)	0.4 mg	0.004 kg
Talc	10.0 mg	0.100 kg

Mix all the above ingredients except 50% of the starch, and compress into slugs using 1 1/2-in. flat-face punches. Grind the slugs using a 16 mesh screen. Transfer to a tumble blender, add the remainder of the Sta-Rx starch, mix for 15 min and compress to weight using 1/2-in. flat-face bevel-edge punches.

Note that this is not intended to be a chewable tablet. Good mouth-feel for antacid chewable tablets can only be achieved through wet granulation. During the wet granulation process some of the soluble components dissolve in the aqueous granulating liquid and coat the particles of the insoluble antacid ingredients to produce a smooth mouth-feel when dried and tableted. Also, for chewable tablets a quantity of mannitol alone or in combination with other soluble sugar compounds (e.g., Di-Pac)—approximately equal to the quantity of antacids—is required for good mouth-feel and chewability.

Example 44: Ferrous Gluconate Tablets

Ingredient	Quantity per tablet
Ferrous gluconate (powder)	325 mg
Dextrose (fine granular)	115 mg
Starch	55 mg
Sta-Rx starch	25 mg
Magnesium stearate	7 mg

Mix the above ingredients, compress into slugs using 1 to 1 1/2-in. flat-face punches; reduce to granules by passing through a 16 mesh screen and compress tablets to weight with 13/32-in. deep cup punches in preparation for coating.

Example 45: Multivitamin Tablets

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Vitamin A (dry stabilized form)	5,000 IU	50×10^6 IU
Vitamin D (dry stabilized form)	400 IU	4×10^6 IU
Vitamin C (ascorbic acid, coated)	75 mg	750.0 g
Vitamin B_1 (thiamine mononitrate)	10 mg	100.0 g
Vitamin B_2 (riboflavin)	2 mg	20.0 g
Vitamin B_6 (pyridoxine hydrochloride)	1 mg	10.0 g
Vitamin B_{12} (cyanocobalamin)	3 μg	30.0 mg
Calcium pantothenate	3 mg	30.0 g
Niacinamide	10 mg	100.0 g
Orange flavor (spray-dried)	5 mg	50.0 g
Mannitol	280 mg	2800.0 g
Sucrose 6×	40 mg	400.0 g
Corn starch	22 mg	220.0 g
Talc	12 mg	120.0 g
Magnesium stearate	7.5 mg	75.0 g

Note: Appropriate overages of all vitamins need to be determined and added in the above formula.

Mix all the ingredients except the corn starch, magnesium stearate, and talc. Slug and screen through a 20 mesh screen. Slug again and screen through a 20 mesh screen. Transfer to a twin-shell blender, add the corn starch, magnesium stearate, and talc; mix for 10 min and compress to weight using 1/2-in. flat-face bevel-edge punches.

Example 46: Prednisone Tablets (5 mg)

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Prednisone USP	5 mg	50.0 g
Calcium sulfate	100 mg	1000.0 g
Sta-Rx starch	20 mg	200.0 g
Microcrystalline cellulose	20 mg	200.0 g

Example 46 (continued)

Ingredient	Quantity per tablet	Quantity per 10,000 tablets
Dicalcium phosphate	12 mg	120.0 g
Sterotex	5 mg	50.0 g
FD&C Yellow Lake No. 6	1.5 mg	15.0 g
Colloidal silica aerogel	1.5 mg	15.0 g

Note: Since many steroid compounds are strongly adsorbed on talc, dicalcium phosphate—having some glidant and lubricating properties—is used in place of talc.

Mix all the ingredients well except for 60 g of dicalcium phosphate and 5 g of silica aerogel which is retained for later addition. Slug the mixture using 1 1/4 to 1 1/2-in. flat-face punches. Reduce the slugs to granules by passing through a 14 mesh screen. Repeat the slugging operation* and pass the resulting slugs through a 20 mesh screen. Mix the remaining 60 g of dicalcium phosphate with the 5 g of silica aerogel; pass through a 100 mesh screen and add to the granulation in a twin-shell blender. Mix for 10 min and compress to weight using 1/4-in. standard concave punches.

A. The Slugging Process

Granulation by slugging is the compressing of dry powders of a tablet formulation with a tablet press having die cavities large enough in diameter to fill quickly and without much difficulty. Usual diameters are from 3/4 to 1 1/4 in., with the greatest thickness that will yield consistently compacted tablets or slugs. The accuracy or condition of the slugs is not too important. They may be poorly formed tablets or compacted masses, except that the more uniform the fill weight and freedom from lamination, the better the slugs and the final granulation. Slugging is often referred to as precompression or double compression. This is correct in referring to the final tablet; but a slug on a double rotary tablet machine may be compressed twice: once on each side. A single or double rotary machine may also be equipped with special cams to precompress the material before the final compression at the pressure rolls. Precompression therefore does not involve slugging in the true sense.

*Double slugging is used to obtain uniform distribution of small amounts of active ingredients in final tablets.

Only sufficient pressure to compact the powder into uniform slugs should be used. The use of excessive pressure in an attempt to force compaction may result in severe lamination or damage to the equipment. Once adequate slugs are produced, they are reduced to appropriate granule size for final compression by screening or milling with various types of size-reduction equipment (such as a Stokes oscillating granulator) or a mill (such as a Fitzpatrick comminutor or a Stokes Tornado mill).

Powders tend to "bridge" and feed spasmodically or sluggishly through hoppers into feed shoes or feed frames. If the powder does bridge or "gap" in the hopper spout to the feed frame, this can often be overcome by attaching a vibrator to the hopper or by placing a mechanical agitator or aerator in the hopper to keep the powder moving continuously. Once this is accomplished, the induced die feeder on most modern machines insures filling of the die cavities, provided they are not unduly small.

The rotary-type machine is more suitable for slugging for three reasons.

1. The die cavities are overfilled and the excess powder is scraped.
2. The feeding principle is continuous as compared to a single-punch machine, which operates in cycles. This helps to keep powders moving continuously and thus minimizes bridging.
3. The compression is more gradual and has a definite dwell time. This improves the slug by allowing entrapped air to escape more easily.

There are many factors which determine how well a material may slug, and a change in any one of these can make a great difference in the slugging operation and the properties of the resulting slugs. These factors are:

1. Compressibility or cohesiveness of the material
2. Compression ratio of the powder: the ratio of the depth of die fill to slug thickness
3. Density of the powder
4. Machine type: rotary or single-punch
5. Machine size or capacity
6. Punch and die size
7. Punch and die clearance
8. Slug thickness
9. Speed of compression
10. Pressure used to produce slug

In slugging, round, flat-faced punches should be used because concave or bevel edges tend to trap air within the slug. The maximum diameter possible should be used. This is done for better feeding rather than for higher production rate. For more uniform feeding and compressing, the thickness of the slugs should not exceed 1/2 in. If difficulties arise, such as laminating, breaking, or sticking of slugs: reduced speed and/or pressure, reduced thickness of the slug, or increased punch clearance may improve the slugs.

Because the powders are fine, the cohesiveness is not as good as that of a granulation, and this causes the slugs to expand almost explosively in some cases, resulting in bursting as well as lamination. Tapered dies are often necessary in such cases. The taper should be 0.010 to 0.020 in. and should start slightly

deeper than the distance where the upper punch enters the die. This also reduces the amount of lubricant required.

The amount of pressure used to form a slug should be less than that required to make the final tablet, if nonporous, smooth tablets are to be made. Crystalline materials, such as aspirin and salt, are exceptions. From 5 to 30 tons $in.^{-2}$ pressure is needed to slug, depending upon the compressibility of the materials. Double slugging (slugging, grinding, and reslugging) is often used to improve the final granulation. Not every material can be slugged—even at pressures up to 50 tons $in.^{-2}$. Examples of such materials are calcium lactate and sodium salicylate.

For each tablet press, there is a maximum pressure that can be used, which varies with the diameter of the die. This maximum pressure chart is shown in Table 13 for the tablet presses more commonly used in slugging.

B. The Pressure Roll Process

The compaction of powders by means of pressure rolls can also be accomplished by a machine called the Chilsonator. The end result is much the same as slugging—in that dry powders are compacted by agglomeration forces alone. Unlike tablet machines, the Chilsonator turns out a compacted mass in a steady, continuous flow at a rate up to 400 kg hr^{-1} at pressures up to 80 tons $in.^{-2}$. This machine utilizes two grooved rollers revolving toward each other. The space between them is controlled by means of hydraulic rams. The speed and the pressure of the rolls on

Table 13

Maximum Pressure Chart for Slugging

Press	Maximum pressure specification (tons $in.^{-2}$)	Maximum pressure at various die diameters (tons $in.^{-2}$)							
		1/2	5/8	3/4	7/8	1	1 1/4	1 1/2	2
Manesty F-3	4	20	13	9	6	4	--	--	--
Stokes B-2	4	20	13	9	66	--	--	--	--
Stokes D-3	7	35	22	15	11	--	--	--	--
Stokes DS-3	10	50	32	22	16	12	9	--	--
Colton Medalist	6	30	18	12	9	7	--	--	--
Colton Monitor	15	--	50	34	25	19	13	--	--
Colton Monarch	10	--	32	22	16	12	9	--	--
Manesty RS-3	10	--	--	45	33	25	18	13	8
Manesty Rotapress	20	--	--	--	--	25	18	13	8
Manesty Betapress	20	--	--	22	16	12	--	--	--
Manesty Express	10	--	--	22	16	--	--	--	--

the powder can be controlled; the rolls are labyrinth-cored for cooling or heating as required for the product characteristics. The powder is fed down between the rollers from a hopper which contains a spiral auger to feed the powder into the compaction zone. After passing between the rollers the compacted mass emerges as a thin sheet or cake which has fallen apart into large aggregates formed under pressure by the grooves in the rollers. These are equivalent to the slugs produced by a tablet press. Like slugs, the aggregates are screened or milled for the production of granules.

The Hutt Compactor is similar to the Chilsonator. It has a hopper mounted above two cylindrical, toothed rollers. The hopper contains an auger which can be operated at variable speed. The rollers are turned by a separate motor and can be operated at variable speed. This equipment can process 200 to 300 kg hr^{-1}, depending upon the powder characteristics. Like the Chilsonator, the Hutt Compactor produces a solid pressed sheet which can be reduced to granules by the usual means.

C. Formulations for Dry Granulation

The excipients used in dry granulation are basically the same as those used in wet granulation or direct compression. However, the powder flow properties do not have to be as good as required for direct compression. Since much higher compaction pressures can be used, excipients that are more difficult to compress can also be used. With dry granulation, it is often possible to compact the active ingredient with a minor addition of lubricant and disintegrating agent, so that the active ingredient would constitute the bulk of the final tablet. This is a major advantage of dry granulation. Fillers that are used in dry granulation include the following: lactose, dextrose, sucrose, microcrystalline cellulose, calcium sulfate, dicalcium phosphate, tricalcium phosphate, and Sta-Rx starch. The other excipients used, such as lubricants, glidants, and disintegrants, are the same as used in wet granulation and direct compression.

VI. Problems in Tablet Manufacture

The production of imperfect tablets having certain noticeable defects causing them to be rejected is annoying and costly. It indicates a lack of proper formulation or difficulties with one or more processing steps, such as lack of control of one or more of the unit processes of manufacturing or incorrect tablet press setting or operation. The imperfections resulting from any of the above situations are designated as follows: binding, sticking, filming, picking, capping, laminating, chipping, and cracking.

A. Binding

Binding is generally due to insufficient lubrication. The resistance of the tablet to ejection due to adherence to the die wall is called binding in the die. Tablets compressed with sufficient lubrication have smooth, glossy edges or sides. When lubrication is insufficient, tablets have rough sides or edges with vertical scratches or score marks caused by the abrasion on ejection. Tablets often crack or chip as

a result of binding. The edges of such tablets are also light in color in the case of colored tablets. With excessive binding, the tablets are cracked and may crumble apart. Preliminary tests should therefore be run on new formulations to assure adequate lubrication. When tablets bind in the dies, the dies should be thoroughly cleaned before starting again. If the binding is not due to high moisture content or worn dies, the addition of the proper lubricant alone will be sufficient to clean the dies.

When the binding is in one or more stations of a rotary press, the punches and dies in question should be compared in dimensions to the tooling that does not cause binding. High-speed operation sometimes causes a film to form in the die which is not evident at normal speeds. This requires modification of the lower punch and die to increase punch-die clearance.

One of the remedies for binding is the use of increased or more efficient lubricant. Coarse granulation can cause lubricant failure. With some formulations, lubricant failure may occur if the granulation is too cold or too warm—causing sticking in the dies. Changing the temperature or the lubricant system may help to eliminate this problem.

Excess moisture in the granulation can also cause binding in the die. Rapid and excessive expansion of the tablet can cause binding, which can be reduced by tapering the dies about two thirds of the expansion. Machine causes of binding are nicked or spread punch tips (especially with bisected punches) and too little pressure. Compression studies should be done to help avoid this problem.

Thus the remedies for binding may be summarized as follows:

1. Increase lubrication.
2. Use more efficient lubrication.
3. Improve method of addition of lubricant, such as by screening the lubricant through an 80 mesh sieve and mixing first with a portion of the fines.
4. Increase moisture or regranulate.
5. Modify granulation: reduce granule size.
6. Increase punch-die clearance.
7. Taper dies.
8. Compress at lower temperature and/or humidity.

B. Sticking

Sticking, also referred to as filming or picking, is usually due to incompletely dried or improperly lubricated granulations. Either of these will allow some of the granulation to stick to the punch faces. These are usually small fragments from the tablet face at first, but the condition becomes progressively worse with larger and larger pieces of tablet being picked from the face as compression continues. Tablets may chip or break if picking occurs on the lower punch or may pull apart from the upper punch. The remedy is to control the moisture in the granulation. Moisture analysis should be done on all granulations, and preliminary tests should be carried out on new formulations to establish maximum tolerated moisture in granulations.

Sticking, filming, or picking happens more often with a single-punch machine because of insufficient pressure or top pressure only. On rotary machines, increasing the pressure, reducing the running speed, and/or increasing

the proportion of binder help to overcome these defects. Also, where possible, the use of light mineral oil as a lubricant is often highly effective. Another approach is the use of highly polished punches or chromium-plated punches. Chromium, because of its smooth, slick characteristics resists sticking and picking.

Filming is a form of sticking. It is the slow buildup of a thin film, at first, of the granulation or a combination of the lubricant with one or more ingredients in the formulation, on the punches under pressure. This is due largely to loss of polish of the punch faces, resulting in dull, imperceptibly roughened punch faces to which small particles of granulation can adhere. Film buildup is also caused by high humidity or high temperature. If the buildup is allowed to progress, tablets from concave and beveled-edge punches eventually fill in punch concavities and become flat, while tablets from flat-faced punches will become concave because of buildup of granulation around the edges of the punch faces. Filming or sticking may be caused by rough or scratched punch faces and nicked punch tips, especially with bisected punches which have been run closely face-to-face, with letters or designs that may be too sharp, or with a concavity too deep for the granulation. Filming may also be caused by oily or waxy materials or too little lubrication.

Filming can be overcome by altering the granulation, changing or decreasing the lubricant, adding an adsorbent (such as microcrystalline cellulose), cleaning or polishing punch faces, and altering designs or lettering on the punch faces. In summary, the remedies for sticking, filming and picking are:

1. Decrease moisture content of the granulation.
2. Change or decrease the lubricant.
3. Increase proportion of binder in the granulation.
4. Add an adsorbent, such as microcrystalline cellulose, silica gel, silica aerogel, or aluminum hydroxide.
5. Clean punch faces with 5% light mineral oil in isopropanol or 5% low-viscosity dimethyl polysiloxane in trichloroethylene.
6. Polish punch faces on lathe with jewelers rouge or fine emery cloth or chromium plate punches.

C. Capping and Lamination

Capping is the defect in which the top or upper segment of the tablet is cracked around the edge or separated as a cap. It is usually due to air entrapped in the die—which is compressed as the punches move together to apply pressure, and which then expands when the pressure is released. This occurrence is common with granulations having a large percentage of fines. Very often new punches and dies have a tendency to cause capping because of the close fit between punch and die wall. The standard clearance of 0.001 in. is sufficient to cause capping. Excess moisture in the granulation or excess lubrication, as well as too little lubrication, may produce capping.

Laminating is caused by the same factors as capping but by exaggerated conditions at high speed. It differs from capping in that tablets split or crack on the sides by air expansion when pressure is released—causing the tablet, when ejected, to come apart or separate in layers. This may also be due to springy, poorly cohesive, or oily granules. In more severe conditions, tablets break apart or tend to explode on ejection. When tablets from a rotary machine cap or laminate

Expansion varies greatly with different types of materials. As the granulation is compressed between the two punches in the die, it expands against the die walls; and as the tablet is being ejected from the die, this expansion is still taking place, with the result that the tablet is forced through a hole whose diameter is smaller than that of the tablet itself. The added friction on the tablet often causes it to cap or laminate. This trouble can easily be recognized by a definite squeak as the tablets are ejected from the dies. On a rotary press, there is usually a pronounced knock also, as the lower punches ride up the ejection cam.

Another method of determining if this is the trouble is to turn the machine over by hand with the handwheel. Usually it will be found that more pressure is required to eject tablets than to actually compress them. In most cases this difficulty can be overcome by tapering the die a few thousandths of an inch as described previously. This allows the tablet to expand without capping, laminating, or breaking.

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This is Exhibit C to the Declaration of Dr. Michael Lipp
Sworn on 2/9/04

Cindy A Sragg

A Notary Public...for taking Affidavits, etc.

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009